Cover Page

CLINICAL STUDY PROTOCOL

NCT04603027

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Cohort, Dose-Ranging Study Investigating the Effect of EDP1815 in the Treatment of Mild to Moderate Plaque Psoriasis

PROTOCOL EDP1815-201
Version 5.0 (Amendment 4), 17 November 2020

Title Page

CLINICAL STUDY PROTOCOL

EudraCT number 2019-004901-28

IND number 19576

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Cohort, Dose-Ranging Study Investigating the Effect of EDP1815 in the Treatment of Mild to Moderate Plaque Psoriasis

PROTOCOL EDP1815-201

Sponsor:	Evelo Biosciences Inc. 620 Memorial Drive, Suite 500 Cambridge, MA 02139 USA
Sponsor Contact:	[redacted]
Sponsor Medical Monitor:	[redacted]
Study Medical Monitor (study participant management):	[redacted]
Version and Date of Protocol:	Version 5.0 (Amendment 4), 17 November 2020
Previous Version and Date of Protocol:	Version 4.1 (Amendment 3.1, Hungary), 27 October 2020 Version 4.0 (Amendment 3), 26 May 2020
Compound Name:	EDP1815
Study Phase:	2

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice.

Protocol Approval – Signatories

Study Title	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Cohort, Dose-Ranging Study Investigating the Effect of EDP1815 in the Treatment of Mild to Moderate Plaque Psoriasis
Protocol Number	EDP1815-201
Protocol Date and Version	17 November 2020; Version 5.0

Protocol accepted and approved by:

Sponsor Signatories

[redacted] Date

Lead Statistician
[redacted] Date

Protocol Amendment 1 – Summary of Major Changes

The study has been amended to enhance the safety of all participants and the safety of potential offspring of male participants.

The major change enhancing the safety of all participants has been made with the addition of a new section. It reads, in its entirety:

11.3.1 Study Halting Criteria

The study will be terminated if any of the following occur:

- **One death considered definitely, probably, or possibly related to the study drug**
- **Two or more subjects with an SAE considered definitely, probably, or possibly related to the study drug**
- **Three or more subjects with grade 3 AEs of the same type considered definitely, probably, or possibly related to the study drug**

The major change affecting the safety of potential offspring of male participants has been made with the addition of a new bullet point to the contraception guidance for male participants in Section 13.1:

- **Have had a vasectomy, and the absence of sperm has been confirmed in the ejaculate.**

Administrative and minor grammatical, editorial, and formatting changes were made for clarification purposes only.

Protocol Amendment 2 – Summary of Major Changes

Please note that Protocol Amendment 2 was not submitted to regulatory authorities or investigative sites.

The study has been amended to reduce the number of cohorts in the study from 3 to 2, to amend the ratio of patients receiving EDP1815 or matching placebo from 3:1 to 2:1, to remove the secondary objectives to evaluate efficacy dose response and optimal dose of EDP1815, to include the option for study visits to be conducted remotely in exceptional circumstances (and where operationally possible), to clarify the addition of BMI calculation, to add IND number and change the study title. Sections 7.9 through 7.10.3.4 were deleted as information was already present in Sections 6.3 through 6.4.3.4.

Administrative and minor grammatical, editorial, and formatting changes were made for clarification purposes only.

The major changes listed above have been made in addition to the edits in the following sections (and the corresponding text in the Protocol Synopsis).

Changes have been marked as follows: new text as **bold** and deleted text as ~~strikethrough~~.

Title Page (and globally, where applicable):

IND number 19576

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Cohort~~, Dose-Ranging~~ Study Investigating the Effect of EDP1815 in the Treatment of Mild to Moderate Plaque Psoriasis.

Section 1:

This Phase 2 study has been designed to investigate the clinical response to treatment with EDP1815 ~~and to identify an optimal dose~~.

Section 2.2:

The secondary objectives of this study are the following:

- ~~To evaluate the efficacy dose response of EDP1815 at Week 16~~

- To evaluate the maximal clinical benefit of EDP1815 at Week 16
- ~~To evaluate the optimal dose of EDP1815 based on efficacy and safety up to Week 16~~
- To evaluate the safety and tolerability of EDP1815 ~~(all dose levels)~~ throughout the study

Section 3.1:

After eligibility is confirmed during the screening period (Section 4.1), participants will be randomly assigned in a 1:1~~:1~~ ratio to ~~one~~**1** of the following ~~3~~ **2** parallel cohorts:

- Cohort 1: 1.6×10^{11} cells of EDP1815 or matching placebo administered as 2 ~~mini tablets in capsules (~~MICs~~)~~, once daily (Section 5.2).
- Cohort 2: 4.8×10^{11} cells of EDP1815 or matching placebo administered as 6 MICs, once daily (Section 5.2).
- ~~Cohort 3: 8.0×10^{11} cells of EDP1815 or matching placebo administered as 10 MICs, once daily (Section 5.2).~~

In each cohort, approximately ~~60~~ **69** participants will be randomly assigned in a ~~3~~**2**:1 ratio to receive either EDP1815 or matching placebo once daily for 16 weeks.

The study design figure (Figure 3.1) was updated accordingly to remove Cohort 3.

Section 3.1.1:

The doses tested in the program are based on predictions from the preclinical data and the clinical and biomarker data obtained in EDP1815-101, the Phase 1 study. All doses tested up to 8.0×10^{11} cells have been equally well tolerated. No clear difference in efficacy was observed between the 1.6×10^{11} cells and the 8.0×10^{11} cells in EDP1815-101 over the 28-day dosing period, but at the 14-day follow up (Day 42) the participants receiving the higher dose had a continued improvement in their psoriasis compared to participants who had received the lower dose. ~~This suggests a more sustained and potentially deeper response in the high dose group. Evelo is therefore proposing to include the highest feasible dose (based on capsule load) in this study to establish the maximum clinical benefit and to assess~~

~~participant acceptability of the doses tested. The dose-response relationships found in this study are expected to enable the selection of appropriate dosing for future studies.~~ **This suggests additional efficacy could be obtained at doses above the dose of 1.6×10^{11} cells. Therefore, 4.8×10^{11} cells will be tested as well as 1.6×10^{11} cells in this study.**

Section 4.1:

Approximately ~~180~~ **138** participants will be enrolled (randomly assigned to treatment) in multiple countries, including (but not limited to) sites in the United States, the United Kingdom, and Poland.

Section 4.2.4:

Participants who withdraw or are withdrawn from the study within 4 weeks of randomization may be replaced in order to have approximately ~~180~~ **138** participants provide at least 4 weeks of postbaseline data.

Section 5.1:

Participants will be randomly assigned at the baseline visit (Visit 2) to 1 of ~~3~~ **2** cohorts (in a 1:1~~:1~~ allocation ratio) that are distinguishable to participants and study staff by the number of capsules administered per once-daily dose. Within ~~each~~ **the** cohort, participants will be randomly assigned in a ~~3~~ **2**:1 allocation ratio to receive either EDP1815 or matching placebo treatment (Section 3.1). Interactive response technology (IRT) will be used to administer the randomization schedule.

Section 6:

The SoA is presented in Table 6 1. Detailed instructions for study site activities will be provided in the study manual. High level descriptions of the study assessments are presented in the subsections of Section 6. **In exceptional circumstances, study assessments may be conducted remotely (ie, at a participant's home), except for baseline, Visit 9, and Visit 10. Remote visits can only occur if operationally possible.**

Section 6.2.3:

A complete physical examination will be conducted, including assessments of the skin and cardiovascular, respiratory, GI, and neurological systems. Height (at screening only) and weight will also be measured and recorded (without shoes, street clothing). **Body mass index will be calculated from the height and weight.** Investigators should pay special attention to clinical signs related to previous serious illnesses.

The SoA (Table 6-1) was also updated to include a footnote clarifying the BMI calculation.

Section 6.4.2:

Systemic exposure following oral EDP1815 dosing is estimated to be very low based on lack of detection in blood (<0.01% of administered dose). However, plasma samples will be taken from all participants for the estimate of systemic EDP1815 levels by PCR with strain-specific primers that can detect EDP1815 specifically, even when other strains of *Prevotella histicola* are present. Any effects of EDP1815 on the gut microbiome will be investigated using 16S ribosomal RNA sequencing, which measures both the presence and quantity of microbes at the genus level. **Sampling will be performed as specified in the SoA (Table 6-1, blood sample for systemic levels of microbes)**.

Section 7.2:

~~As a further supplementary analysis, a dose-response model will be fitted using Bayesian techniques as fully described in Section 7.8.1. This model will be fitted for the primary endpoint of percentage change from baseline at Week 16. Data collected after discontinuation of treatment will be considered missing and imputed using an LOCF approach in order to include all participants who had at least one evaluable on-treatment percentage change from baseline in PASI score available. A sensitivity analysis, including only participants who have evaluable percentage change from baseline in PASI score at Week 16 will also be performed.~~

~~If the results of the supportive MMRM analyses show substantial differences to the primary MMRM analysis, further sensitivity analyses may also be performed excluding data following protocol deviations which may affect efficacy or including all data collected during the study regardless of treatment discontinuation.~~

Section 7.5:

The sample size of ~~180~~ **138** participants in total, has been chosen to explore the tolerability and safety of EDP1815. "…"

Participants in the placebo arm of each cohort will be pooled for the statistical analysis in order to compare active and control arms resulting in ~~45~~ **46** participants ~~will be~~ randomized to each treatment group (pooled placebo, EDP1815 1.6×10^{11} cells, **and** EDP1815 4.8×10^{11} cells~~, and EDP1815 8.0×10^{11} cells~~). Assuming that no more than 15% of participants will discontinue treatment before the Week 16 visit, at least ~~38~~ **39** participants in each treatment group are expected **to** provide data through the Week 16 visit.

Each pairwise comparison between placebo and active dose would be expected to have more than 90% power to detect a difference between the treatment groups at the 5% significance level under the assumption that pooling the placebo groups is a valid strategy. If the ~~3~~ **2** placebo cohorts are considered to be too heterogeneous for pooling into a single reference group, the power to detect a difference in each pairwise comparison between active and placebo doses within a cohort falls to approximately ~~70~~ **80**%.

Section 7.7:

If the placebo groups from the ~~3~~ **2** cohorts are found to be too heterogeneous to be pooled (Section 7.8.1), the primary and secondary analyses will be performed using within-cohort comparisons of active and placebo treatments, and summary tables may also be produced by cohort.

Section 7.8.1:

The assumption that the ~~3~~ **2** cohorts of placebo participants can be pooled into a single placebo group to be used as a control for all active doses will be examined using mean (±SD) plots of percent change in PASI score against time. A decision will be made by the Evelo study team on whether the pooling strategy is appropriate.

The primary analysis will be performed using an MMRM. The model will include parameters for treatment*visit and baseline PASI score*visit interactions. Body mass index, gender, and other baseline covariates will also be considered and included as parameters if found to be significant ($p<0.05$). The model will not include an intercept. Visit will consist of 6 levels

(Weeks 1, 2, 4, 8, 12 and 16) and treatment will consist of ~~4~~ **3** levels (pooled placebo, EDP1815 1.6 **x 10^{11} cells,** and EDP1815 4.8 x **10^{11} cells** ~~and EDP1815 8.0 x~~) if the placebo pooling strategy is considered appropriate or ~~6~~ **4** levels (Placebo **matching** 1.6 **x 10^{11} cells**, Placebo **matching** 4.8 x **10^{11} cells**, EDP1815 1.6 x 10^{11} cells**,** and EDP1815 4.8 x 10^{11} cells ~~and EDP1815 8.0x~~) if the placebo pooling strategy is not considered appropriate. "…"

If the assumption of similarity between the ~~3~~ **2** placebo cohorts is considered appropriate, the placebo cohorts will be pooled, and a single placebo control group will be used for the pairwise differences for each active dose to placebo. "…"

~~If the assumption of similarity between the placebo cohorts is supported, a supplementary analysis will be performed on the percent change from baseline to Week 16 in PASI score using a dose response model on the pooled cohorts. The log-linear, 3-parameter and 4-parameter Emax models will be fitted and compared, with the best fitting model (lowest DIC) selected for use in the outputs.~~

~~The dose-response model will be fitted to the data using Bayesian techniques with non-informative priors for E0 and Emax and an FUP for ED50 (3- and 4-parameter models only) and the slope parameter m (4-parameter model only). The rationale for this choice of inference is that the FUP shrinks the dose-response towards a flat line throughout the dose range, therefore providing more conservative estimates of the dose-response relationship compared to maximum likelihood (Bornkamp 2014). The models will be fully described in the SAP.~~

~~Based on the selected model, the posterior mean with associated 95% HDP CrI, for the difference from placebo for each active dose will be produced for the pairwise differences between each active dose and placebo, together with the posterior mean and 95% HDP CrI of the treatment difference from placebo for each active dose and posterior probabilities that difference from placebo is less than 0, -20%, -30% and -50%.~~

Section 7.8.2:

All secondary analyses will be performed either using the pooled placebo group if the assumption of similarity for the placebo cohorts is considered appropriate or using the ~~3~~ **2** cohort-level placebo groups if it is not considered appropriate.

Section 7.9:

~~Pregnancy is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation or up to 28 days after the final dose of study drug must be reported to [redacted] by phone or email, within 2 weeks of learning of its occurrence. [redacted] will send the Exposure in Utero Form to the site for completion within 24 hours. This form should be completed and returned to [redacted] within 24 hours of receipt. The pregnancy must be followed up until the first "well baby visit"(or similarly purposed visit 6 to 8 weeks postpartum) to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the participant was discontinued from the study. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, congenital anomaly, ectopic pregnancy), the investigator should follow the procedures for reporting an SAE. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.~~

~~Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the participant has completed the study, and considered by the investigator as possibly related to the study treatment, must be promptly reported to [redacted].~~

Section 7.10:

~~Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital sign measurements), including those that worsen from baseline or are clinically significant in the medical and scientific judgment of the investigator, are to be recorded as AEs or SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition, are **not** to be reported as AEs or SAEs.~~

~~Standard laboratory analyses to understand safety and tolerability include the following:~~

- ~~Blood or plasma analytes: urea, creatinine, sodium, potassium, ALT, AST, total and direct bilirubin, CRP, creatine kinase, fasting glucose, fasting lipid panel (total cholesterol, HDL, LDL, triglycerides)~~

- ~~Hematologic analyses: full blood count, including hemoglobin, MCV, MCH, MCHC, hematocrit, percent reticulocytes, platelet count; differential white blood cell count including neutrophils, lymphocytes, monocytes, and eosinophils~~

- ~~Urinalysis by dip stick: protein, blood, glucose, ketones, bilirubin, pH, nitrites, and specific gravity~~

~~Other screening tests include the following:~~

- ~~Serology (HIV antibody, HBsAg, and HCV antibody)~~

- ~~Serum pregnancy test (HCG) at screening, urine test thereafter~~

~~Blood samples for assessment of fasting blood glucose and lipid panel will be obtained after the participant has fasted for at least 8 hours.~~

~~A central laboratory (or specialized central laboratories) will be used for all laboratory analyses. Details of sample collection and handling procedures will be provided in the study manual.~~

~~The investigator must review the laboratory reports, document this review, and record any clinically relevant changes occurring during the study. If the laboratory reports are not transferred electronically, the values must be filed with the source information (including reference ranges). In most cases, clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.~~

~~All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.~~

~~All protocol-required laboratory assessments, as defined in this section, must be conducted in accordance with the laboratory manual and the SoA (Table 6-1). If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.~~

Section 7.10.1:

~~The planned maximum amount of blood collected from each participant over the duration of the study is less than 130 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. The planned maximum amount of blood collected from each participant at a single visit is less than 46mL, and the planned maximum amount of blood collected from each participant over 30 days is less than 58 mL.~~

Section 7.10.2:

~~Systemic exposure following oral EDP1815 dosing is estimated to be very low based on lack of detection in blood (<0.01% of administered dose). However, plasma samples will be taken from all participants for the estimate of systemic EDP1815 levels by PCR using EDP1815-specific primers. Sampling will be performed as specified in the SoA (Table 6-1, blood sample for systemic levels of microbes).~~

~~Systemic exposure of EDP1815 will be measured using specific PCR with strain specific primers which can detect EDP1815 specifically even when other strains of *Prevotella histicola* are present. Any effects of EDP1815 on the gut microbiome will be investigated using 16S ribosomal RNA sequencing, which measures both the presence and quantity of microbes at the genus level.~~

Section 7.10.3:

~~Procedures for sample collection, processing, storage, and shipment will be detailed in the study manual. Biomarkers are exploratory endpoints and analytical results for biomarkers will not be included in the CSR. They will be reported separately from the CSR.~~

~~Digital photographs should be taken of up to 6 lesion sites that have a lesion area ≥2 cm × 2 cm at baseline. The same locations photographed at baseline should be followed~~

~~throughout the study for each participant. Procedural details for digital photography will be provided in the study manual.~~

Section 7.10.3.1:

~~Standard histology will be performed on skin plaque biopsies (including epidermal thickness, basal mitotic counts and immune cell infiltrates, immunohistochemistry) from approximately 15 participants in each cohort. Details will be provided in the study manual. The histologic evaluations are exploratory and are outside the scope of the CSR.~~

Section 7.10.3.2:

~~An mRNA transcription analysis will be performed on the skin plaque biopsies.~~

Section 7.10.3.3:

~~Blood samples will be stimulated ex vivo and analyzed for levels of cytokines and chemokines, including IL-1 beta, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p40, IL-17A, TNFα, and IFNγ.~~

Section 7.10.3.4:

~~The microbiome composition of stool samples will be assessed by 16S ribosomal RNA sequencing, which looks at the diversity and abundance of microbes in the colonic microbiome (Human Microbiome Project Consortium 2012). EDP1815 is not expected to alter the composition of the microbiome, but it is being evaluated as a safety biomarker.~~

Protocol Amendment 3 – Summary of Major Changes

The study has been amended to increase the number of cohorts in the study from 2 to 3, to adjust the doses per cohort, to add secondary objectives to evaluate efficacy dose response and optimal dose of EDP1815, to change some exploratory endpoints to be secondary endpoints, to update the criteria by which AE severity are rated, to update the sponsor medical monitor details, and to change the study title.

Administrative and minor grammatical, editorial, and formatting changes were made for clarification purposes only.

The major changes listed above have been made in addition to the edits in the following sections (and the corresponding text in the Protocol Synopsis).

Changes have been marked as follows: new text as **bold** and deleted text as ~~strikethrough~~.

Title Page (and globally, where applicable):

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Cohort**, Dose-Ranging** Study Investigating the Effect of EDP1815 in the Treatment of Mild to Moderate Plaque Psoriasis.

Section 1:

Evelo Biosciences Inc. (Evelo) is developing **medicines based on** ~~monoclonal~~ single strains of bacteria as a new class of therapeutic agents ~~known as monoclonal microbials. Monoclonal microbials~~. **These therapeutic agents** are human commensal organisms that offer the potential of systemic immune system modulation following oral administration, without systemic exposure. "…"

Several studies (de Groot et al 2017; Hindson et al 2017; Yan et al 2017; Felix et al 2018) suggest that host-microbe interactions in the gut, and particularly in the small intestine, can influence systemic inflammation. Evelo is seeking to develop oral anti-inflammatory medicines based on this emerging science. Preclinical data confirms that individual strains of microbes exhibit unique pharmacological profiles. This is thought to be based on multiple distinct microbial structural pattern motifs interacting with varying combinations of host pattern recognition receptors **in small intestinal epithelium**.

Studies of EDP1815 in vitro in a range of human and mouse assays and studies in vivo in model symptoms support the use of EDP1815 in the treatment of inflammatory diseases including psoriasis (Evelo Biosciences 2019). EDP1815 increases secretion of anti-inflammatory cytokines such as IL-10**, IL-1RA,** and IL-27 from human immune cells, while inducing minimal production of pro-inflammatory cytokines such as IL-6, TNFα, and IFNγ.

Oral administration of EDP1815 to mice results in striking pharmacodynamic effects on animal models of delayed-type hypersensitivity, fluorescein isothiocyanate cutaneous hypersensitivity, collagen-induced arthritis (Marietta et al 2016) and experimental acute encephalomyelitis (Mangalam et al 2017). The high degree of consistency of both effect and dose suggests the potential for clinical benefit across multiple **type 1, type 2, and type 3** ~~immuno~~inflammatory conditions. No potentially related adverse effects were seen in the animals used in these experiments with daily dosing for up to 3 weeks or with alternate day dosing for over 7 weeks. Immunophenotyping ex vivo in these models shows increased regulatory T cell numbers and regulatory dendritic cells in spleen and mesenteric lymph nodes, as well as decreases in pro-inflammatory cytokines such as IL-23p40, IL-17, **TNFα, IL-6,** and IL-13. Treatment also led to enhancement of gut intestinal barrier integrity, which is often disrupted in patients with inflammatory diseases. These effects on immune parameters have been observed both within and outside the GI tract, which demonstrates that host-microbe interactions in the gut can affect the immune response in peripheral tissues.

Psoriasis is a chronic immune-mediated **type 1/3** inflammatory skin disease in which hyperactive T cells trigger excessive keratinocyte proliferation. "…"

This Phase 2 study has been designed to investigate the clinical **safety and efficacy of** ~~response to treatment with~~ EDP1815 **and to identify an optimal dose**.

Section 2:

All objectives are related to understanding the **safety, efficacy, and dose** effects of EDP1815 treatment of mild to moderate plaque psoriasis in adult participants (Section 4.1).

Section 2.1:

The primary objective of this study is to evaluate the **safety and** efficacy of **3 different doses of** EDP1815 for the treatment of psoriasis following daily dosing for 16 weeks.

Section 2.2:

The secondary objectives of this study are the following:

- **To evaluate the efficacy dose response of EDP1815 at Week 16**
- To evaluate the maximal clinical benefit of EDP1815 at Week 16
- **To evaluate the optimal dose of EDP1815 based on efficacy and safety up to Week 16**
- To evaluate the safety and tolerability of EDP1815 **(all dose levels)** throughout the study

Section 2.3:

The exploratory objectives of this study are the following:

- To evaluate the time to onset of clinical response to EDP1815
- To evaluate the effect of EDP1815 treatment on patient-reported outcomes **including quality of life and pain**
- To evaluate the effect of EDP1815 treatment on biomarkers in blood
- To evaluate the effect of EDP1815 treatment on biomarkers in skin plaques
- To evaluate the effect of EDP1815 treatment on fecal microbiome composition

Section 3.1:

After eligibility is confirmed during the screening period (Section 4.1), participants will be randomly assigned in a 1:1**:1** ratio to 1 of the following **3** ~~2~~ parallel cohorts:

- Cohort 1: **0.8**~~1.6~~ × 10^{11} cells of EDP1815 or matching placebo administered as **1 PIC** ~~2 MICs~~, once daily (Section 5.2).
- Cohort 2: **3.2**~~4.8~~ × 10^{11} cells of EDP1815 or matching placebo administered as **4 PICs**~~6 MICs~~, once daily (Section 5.2).
- **Cohort 3: 8.0 × 10^{11} cells of EDP1815 or matching placebo administered as 10 PICs, once daily (Section 5.2).**

In each cohort, approximately **75**~~69~~ participants will be randomly assigned in a 2:1 ratio to receive either EDP1815 or matching placebo once daily for 16 weeks.

The study design figure (Figure 3.1) was updated accordingly to add Cohort 3.

Section 3.1.1:

The doses tested in the program are based on predictions from the preclinical data and the clinical and biomarker data obtained in EDP1815-101, the Phase 1 study. All doses tested up to 8.0 × 10^{11} cells have been equally well tolerated. No clear difference in efficacy was observed between the 1.6 × 10^{11} cells and the 8.0 × 10^{11} cells in EDP1815-101 over the 28-day dosing period, but at the 14-day follow up (Day 42) the participants receiving the higher dose had a continued improvement in their psoriasis compared to participants who had received the lower dose. This suggests **a more sustained and potentially deeper response in the high dose group. Evelo is therefore proposing to include the lowest and highest feasible doses (based on capsule load) in this study to establish the dose response, the maximum clinical benefit, and to assess participant tolerability and acceptability of the doses tested.** ~~additional efficacy could be obtained at doses above the dose of 1.6 × 10^{11} cells. Therefore, 4.8 × 10^{11} cells will be tested as well as 1.6 × 10^{11} cells in this study.~~

Section 4.1:

Approximately **225**~~138~~ participants will be enrolled (randomly assigned to treatment) in multiple countries, including (but not limited to) sites in the United States, the United Kingdom, and Poland.

Section 4.1.1:

4. Have mild to moderate plaque psoriasis with plaque covering body surface area (BSA) of ≥3% and ≤10% and meet **both** ~~at least 1~~ of the following additional criteria:
    a. PASI score of ≥6 and ≤15~~.~~**, and**
    b. PGA score of 2 or 3.

    All parameters in this criterion should be reconfirmed at baseline visit prior to randomization.

Section 4.1.2:

10. Have used topical medications/treatments that could affect psoriasis or PGA evaluation (including [but not limited to] high- and mid-potency corticosteroids [Appendix 13.2], anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, picrolimus, and tacrolimus) within 2 weeks of the first administration of study drug. Topical unmedicated emollients **and low-potency topical corticosteroids** are not excluded.

Section 4.2:

A participant may discontinue from the study drug or withdraw from the study for any of the following reasons:

1. The participant does not meet the protocol inclusion or exclusion criteria.
2. The participant is noncompliant with the protocol.
3. The participant experiences treatment failure, demonstrated by the participant commencing an oral agent, biological, or **intermediate or** high-**potency** ~~dose~~ topical therapy for plaque psoriasis.
4. "..."

Section 4.2.4:

Participants who withdraw or are withdrawn from the study within 4 weeks of randomization may be replaced in order to have approximately **225**~~138~~ participants provide at least 4 weeks of postbaseline data.

Section 5.1:

Participants will be randomly assigned at the baseline visit (Visit 2) to 1 of **3**~~2~~ cohorts (in a 1:1**:1** allocation ratio) that are distinguishable to participants and study staff by the number of capsules administered per once-daily dose. Within the cohort, participants will be randomly assigned in a 2:1 allocation ratio to receive either EDP1815 or matching placebo treatment (Section 3.1). Interactive response technology (IRT) will be used to administer the randomization schedule.

Section 5.3:

The EDP1815 drug product is ~~a blend of freeze-dried powder of *P histicola* and excipients.~~

~~For this study, EDP1815 is formulated as multiple~~ **available as** enteric-coated **HPMC hard capsules in** ~~minitablets of EDP1815 drug product filled into~~ Swedish-Orange **color** ~~HPMC capsules (MICs)~~. **The EDP1815 PIC consists of freeze-dried powder of *P histicola*, mannitol, magnesium stearate, and colloidal silicon dioxide.** ~~The excipients include mannitol, colloidal silicon dioxide, hydroxypropyl cellulose, crospovidone, and magnesium stearate.~~ Each EDP1815 **PIC**~~MIC~~ contains 8.0×10^{10} cells of *P histicola*.

The matching placebo **is** ~~MICs are~~ identical in appearance but do not contain *P histicola* or any other bacteria. The placebo excipients include ~~mannitol,~~ microcrystalline cellulose~~, colloidal silicon dioxide, sodium starch glycolate,~~ and magnesium stearate.

Section 5.4.1:

EDP1815 **PICs**~~MICs~~ and matching placebo will be prepared in blister wallets of 10 ~~or 20~~ capsules ~~each (cohort dependent)~~. Blister wallets will be packaged in packs that contain approximately 1 week's supply of study drug for 1 randomized participant, identified by a numeric code. When appropriate for the interval between study visits, multiple packs will be assigned and dispensed for each participant throughout the treatment period.

Section 5.8.2:

Anti-histamines and acetaminophen/paracetamol following labeled dosing instructions are permitted for use at any time during the study. Topical unmedicated emollients and low-potency topical steroids are also permitted if participants were already using them as part of their care prior to study entry (exclusion criterion #10, Section 4.1.2). **Participants will be advised to continue to use these therapies as they were prior to study entry.**

Non-live vaccines are permitted in this study.

Section 5.8.2.1:

Prior therapies restricted for participants eligible for this study as detailed in the exclusion criteria (Section 4.1.2) are prohibited concomitant therapy during the study.

Live or live-attenuated vaccines are contra-indicated in this study.

Section 6:

Footnote h was amended in the SoA (Table 6-1):

[h] Blood pressure, pulse, respiratory rate, and ~~oral~~ temperature are to be checked on the morning of the visit.

A new footnote was added in the SoA (Table 6-1):

[n] Inclusion criterion #4 (mild to moderate plaque psoriasis with plaque covering BSA of ≥3% and ≤10%, PASI score of ≥6 and ≤15, and PGA score of 2 or 3) should be reconfirmed at the baseline visit prior to randomization.

Participants meeting eligibility criteria at screening will return to the study site on Day 1. The PASI, BSA involvement, and PGA scores must be available **to reconfirm eligibility** prior to randomization and administration of the first dose of study drug on Day 1 (Visit 2).

Section 6.2.1.2:

If the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor **(or designee)**.

Section 6.2.1.2.1:

The severity, or intensity, of an AE refers to the extent to which an AE affects the participant's daily activities **or their health**. The intensity of the AE will be rated **in accordance with the CTCAE version 5.0**. ~~as mild, moderate, or severe using the following criteria:~~

~~**Mild:** These events require minimal or no treatment and do not interfere with the participant's daily activities.~~

~~**Moderate:** These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning.~~

~~**Severe:** These events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment Severe events are usually incapacitating.~~

Section 6.2.1.3:

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes the following:

- "..."
- **Lot/batch number**
- Any required treatment or evaluations
- Action taken with the study drug due to the event
- Outcome

Section 6.2.4:

Blood pressure, pulse rate, respiratory rate, and ~~oral~~ temperature will be assessed. Blood pressure and pulse measurements will be assessed in a sitting position with a completely automated device. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, mobile phones).

Section 7.1:

~~The primary estimand will be the effect of EDP1815 on the percent change in PASI score from baseline to Week 16 in the mITT set of all treated participants, regardless of deviations from the protocol. Only data collected while on treatment will be used to account for the intercurrent event of treatment discontinuation (hypothetical strategy based on adherence to treatment only). The posterior mean difference between each active dose and the pooled placebo group will be estimated.~~

~~For the primary analysis, 2 supportive estimands will also be considered:~~

- ~~To assess the impact of intercurrent events related to protocol deviations believed to impact efficacy, a supportive analysis will be performed where all data collected after any such identified protocol deviations will be excluded. Participants who had a protocol deviation believed to impact efficacy prior to the first dose of treatment (hypothetical strategy based on adherence to treatment and the aspects of the protocol which impact efficacy) will be completely excluded from this analysis.~~

- ~~To assess the impact of treatment discontinuation, a supportive analysis will be performed in which all data collected during the study, including any data collected after treatment discontinuation will be included (treatment policy strategy).~~

~~Estimands for the analyses of all secondary endpoints are shown in Table 7-1.~~

Table 7-1 Summary of Secondary Estimands

~~**Population of interest**~~	~~**Endpoint**~~	~~**Consideration of intercurrent events**~~	~~**Summary measure**~~
~~mITT set~~	~~Mean change from baseline in PASI Score at Week 16~~	~~To include all data collected prior to treatment discontinuation, regardless of protocol deviations~~	~~Posterior mean difference between each active treatment group and pooled placebo group~~
~~mITT set~~	~~Achievement of PASI 50 at Week 16~~	~~To include all data collected prior to treatment discontinuation, regardless of protocol deviations~~	~~Posterior odds ratio for response between each active treatment group and pooled placebo group~~
~~mITT set~~	~~Achievement of PASI 75, PASI 90 and PASI 100 at Week 16~~	~~To include all data collected prior to treatment discontinuation, regardless of protocol deviations~~	~~Proportion of response for each endpoint in each treatment group~~
~~mITT set~~	~~Achievement of PGA of 0 or 1 with a ≥2 point improvement from baseline at Week 16~~	~~To include all data collected prior to treatment discontinuation, regardless of protocol deviations~~	~~Posterior odds ratio for response between each active treatment group and pooled placebo group~~
~~mITT set~~	~~Achievement of PGA of 0 at Week 16~~	~~To include all data collected prior to treatment discontinuation, regardless of protocol deviations~~	~~Posterior odds ratio for response between each active treatment group and pooled placebo group~~
~~mITT set~~	~~Mean change from baseline in PGA×BSA at Week 16~~	~~To include all data collected prior to treatment discontinuation, regardless of protocol deviations~~	~~Posterior mean difference between each active treatment group and pooled placebo group~~
~~mITT set~~	~~Mean change from baseline in LSS at Week 16~~	~~To include all data collected prior to treatment discontinuation, regardless of protocol deviations~~	~~Posterior mean difference between each active dose and pooled placebo group~~

Section 7.1.1 (previously Section 7.2):

The primary estimand will be the effect of EDP1815 on the percent change in PASI score from baseline to Week 16 in the mITT set of all treated participants, regardless of deviations from the protocol. Only data collected while on treatment will be used to account for the intercurrent event of treatment discontinuation (hypothetical strategy based on adherence to treatment only). The posterior mean difference between each active dose and the pooled placebo will be estimated. ~~The primary efficacy endpoint is the percent change from baseline in PASI score at Week 16.~~

Percent change from baseline in PASI score at each visit will be calculated as:

100*(PASI score at Visit – baseline PASI score) / baseline PASI score.

A negative percentage change from baseline will indicate an improvement.

For the primary analysis, 2 supportive estimands will also be considered:

- **To assess the impact of intercurrent events related to protocol deviations believed to impact efficacy, a supportive analysis will be performed where all data collected after any such identified protocol deviations will be excluded. Participants who had a protocol deviation believed to impact efficacy prior to the first dose of treatment (hypothetical strategy based on adherence to treatment and the aspects of the protocol which impact efficacy) will be completely excluded from this analysis.**

- **To assess the impact of treatment discontinuation, a supportive analysis will be performed in which all data collected during the study, including any data collected after treatment discontinuation will be included (treatment policy strategy).**

~~For the primary analysis, the mITT set with all data collected prior to treatment discontinuation will be used, regardless of any protocol deviations.~~

"..."

Supportive analyses will also be performed in the same manner, using the 2 alternative estimands as defined **above**~~in Section 7.1.1~~. These will explore the possible impact of the intercurrent events of treatment discontinuation and events relating to protocol deviations that may have an impact on efficacy.

Section 7.1.2 (previously Section 7.3):

~~The secondary efficacy endpoints are:~~

- ~~Mean change from baseline in PASI score at Week 16~~
- ~~Percentage of participants achieving PASI 50, PASI 75, PASI 90 and PASI 100 at Week 16~~
- ~~Percentage of participants achieving PGA of 0 or 1 with a ≥2-point improvement at Week 16~~

- ~~Percentage of participants achieving PGA of 0 at Week 16~~
- ~~Mean change from baseline in PGA×BSA score at Week 16~~
- ~~Mean change from baseline in LSS at Week 16.~~

~~All summaries and analyses of interest will be performed on the mITT set, with data collected after discontinuation of treatment excluded, without consideration of any protocol deviations.~~

Estimands for the analyses of all secondary endpoints are shown in Table 7-1.

Table 7-1 Summary of Secondary Estimands

Population of interest	Endpoint	Consideration of intercurrent events	Summary measure
mITT set	Mean percentage change from baseline in PASI Score at Weeks 4, 8, and 12	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active treatment group and pooled placebo at each visit
mITT set	Mean absolute change from baseline in PASI Score at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active treatment group and pooled placebo at each visit
mITT set	Achievement of PASI-50 at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior odds ratio for response between each active treatment group and pooled placebo at each visit
mITT set	Time to first achievement of PASI-50	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Hazard ratio for each active group versus placebo
mITT set	Achievement of PASI-75, PASI-90 and PASI-100 at Week 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Proportion of response for each endpoint in each treatment group at each visit
mITT set	Achievement of PGA of 0 or 1 with a ≥2-point improvement from baseline at Week 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior odds ratio for response between each active treatment group and pooled placebo
mITT set	Achievement of PGA of 0 at Week 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior odds ratio for response between each active treatment group and pooled placebo
mITT set	Mean percentage change from baseline in PGA×BSA at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active treatment group and pooled placebo at each visit

Population of interest	Endpoint	Consideration of intercurrent events	Summary measure
mITT set	**Mean absolute change from baseline in PGA×BSA at Weeks 4, 8, 12, and 16**	**To include all data collected prior to treatment discontinuation, regardless of protocol deviations**	**Posterior mean difference between each active treatment group and pooled placebo at each visit**
mITT set	**Mean percentage change from baseline in LSS at Weeks 4, 8, 12, and 16**	**To include all data collected prior to treatment discontinuation, regardless of protocol deviations**	**Posterior mean difference between each active dose and pooled placebo at each visit**
mITT set	**Mean absolute change from baseline in LSS at Weeks 4, 8, 12, and 16**	**To include all data collected prior to treatment discontinuation, regardless of protocol deviations**	**Posterior mean difference between each active dose and pooled placebo at each visit**
mITT set	**Mean percentage change from baseline in DLQI score at Weeks 4, 8, 12, and 16**	**To include all data collected prior to treatment discontinuation, regardless of protocol deviations**	**Posterior mean difference between each active dose and pooled placebo at each visit**
mITT set	**Mean absolute change from baseline in DLQI score at Weeks 4, 8, 12, and 16**	**To include all data collected prior to treatment discontinuation, regardless of protocol deviations**	**Posterior mean difference between each active dose and pooled placebo at each visit**
mITT set	**Mean percentage change from baseline in mNAPSI total score at Weeks 4, 8, 12, and 16**	**To include all data collected prior to treatment discontinuation, regardless of protocol deviations**	**Posterior mean difference between each active dose and pooled placebo at each visit**
mITT set	**Mean absolute change from baseline in mNAPSI total score at Weeks 4, 8, 12, and 16**	**To include all data collected prior to treatment discontinuation, regardless of protocol deviations**	**Posterior mean difference between each active dose and pooled placebo at each visit**

Section 7.2 (previously Section 7.4):

The exploratory endpoints include the following:

- ~~Mean percentage change from baseline in PASI score at Weeks 4, 8 and 12~~
- ~~Mean change from baseline in PASI score at Weeks 4, 8, and 12~~
- Percentage of participants achieving PASI-50, PASI-75, PASI-90, and PASI-100 at Weeks 4, 8, and 12
- ~~Time to first achievement of PASI 50~~
- Percentage of participants achieving PGA of 0 or 1 with a ≥2-point improvement at Weeks 4, 8, and 12

- Percentage of participants achieving PGA of 0 at Week**s 4, 8, and** 12
- ~~Mean change from baseline in PGA×BSA score at Weeks 4, 8, and 12~~
- ~~Mean change from baseline in LSS at Weeks 4, 8 and 12~~
- Mean change from baseline in ~~DLQI and~~ PSI quality of life scores at Weeks 12 and 16
- **Mean percentage change from baseline in PSI quality of life scores at Weeks 12 and 16**
- Mean change from baseline in Pain and Fatigue scores at Weeks 4, 8, 12, and 16
- **Mean percentage change from baseline in Pain and Fatigue scores at Weeks 4, 8, 12, and 16**
- ~~Mean change from baseline in mNAPSI total score at Weeks 4, 8, 12 and 16~~
- Mean change from baseline in fasting blood glucose and fasting lipid panel at Weeks 8 and 16

Section 7.3 (previously Section 7.5):

The sample size of **225**~~138~~ participants in total, has been chosen to explore the tolerability and safety of EDP1815. "…"

Participants in the placebo arm of each cohort will be pooled for the statistical analysis in order to compare active and control arms resulting in **75 participants randomized to the pooled placebo group and 50**~~46~~ participants randomized to each **active** treatment group (~~pooled placebo,~~ EDP1815 **0.8**~~1.6~~ × 10^{11} cells, ~~and~~ EDP1815 **3.2**~~4.8~~ × 10^{11} cells**, and EDP1815 8.0 × 10^{11} cells**). Assuming that no more than 15% of participants will discontinue treatment before the Week 16 visit, at least **42 active and 21 placebo**~~39~~ participants in each ~~treatment group~~ **of the 3 cohorts** are expected **to** provide data through the Week 16 visit.

Each pairwise comparison between **pooled** placebo and active dose would be expected to have more than **95**~~90~~% power to detect a difference between the treatment groups at the 5%

significance level under the assumption that pooling the placebo groups is a valid strategy. If the **3**~~2~~ placebo cohorts are considered to be too heterogeneous for pooling into a single reference group, the power to detect a difference in each **within-cohort** pairwise comparison between active and placebo doses ~~within a cohort falls to approximately~~ **would be greater than** 80%.

Section 7.4 (previously Section 7.6):

mITT set: The mITT set will consist of all participants who were randomized to treatment and who received at least one dose of study treatment. **Participants who withdraw from the study before the end of Week 4 and are replaced will be included in this analysis set. All** analyses using the mITT will group participants according to randomized treatment.

PPS: The PPS will consist of all mITT participants who **were not replaced (following study withdrawal before the end of Week 4) and who** do not have a protocol deviation ~~which~~ **that** may impact efficacy with a start date for the deviation before initiation of study treatment. "..."

Section 7.5 (previously Section 7.7):

If the placebo groups from the **3**~~2~~ cohorts are found to be too heterogeneous to be pooled (Section 7.6.1), the primary and secondary analyses will be performed using within-cohort comparisons of active and placebo treatments, and summary tables may also be produced by cohort.

Section 7.6 (previously Section 7.8):

Statistical analysis will be performed using SAS software Version 9.3 or later.

In addition to the inferential analyses described in Sections 7.6.1 and 7.6.2, descriptive statistics will be provided to summarize all endpoints by treatment group.

Section 7.6.1 (previously Section 7.8.1):

The assumption that the **3**~~2~~ cohorts of placebo participants can be pooled into a single placebo group to be used as a control for all active doses will be examined using mean (±SD)

plots of percent change in PASI score against time. A decision will be made by the Evelo study team on whether the pooling strategy is appropriate.

The primary analysis will be performed using a~~n~~ **Bayesian** MMRM. The model will include parameters for treatment*visit and baseline PASI score*visit interactions. Body mass index, gender, and other baseline covariates will also be considered and included as parameters if found to be significant ($p<0.05$). The model will not include an intercept. Visit will consist of 6 levels (Weeks 1, 2, 4, 8, 12, and 16) and treatment will consist of **4**~~3~~ levels (pooled placebo, EDP1815 **0.8**~~1.6~~ × 10^{11} cells, **EDP1815 3.2 × 10^{11} cells,** and EDP1815 **8.0**~~4.8~~ × 10^{11} cells) if the placebo pooling strategy is considered appropriate or **6**4 levels (Placebo matching **EDP1815 0.8**~~1.6~~ × 10^{11} cells, Placebo matching **EDP1815 3.2**~~4.8~~ × 10^{11} cells, **Placebo matching** EDP1815 **8.0**~~1.6~~ × 10^{11} cells, ~~and~~ EDP1815 **0**4.8 × 10^{11} cells**, EDP1815 3.2 × 10^{11} cells, and EDP1815 8.0 × 10^{11} cells**) if the placebo pooling strategy is not considered appropriate. "…"

If the assumption of similarity between the **3**~~2~~ placebo cohorts is considered appropriate, the placebo cohorts will be pooled, and a single placebo control group will be used for the pairwise differences for each active dose to placebo. If the assumption of similarity is considered inappropriate, each placebo dose will be included in the model as a separate dose level and pairwise comparisons between each active dose and placebo will be performed using only the matching placebo dose data for the relevant active dose.

The adjusted posterior mean percentage change from baseline and the associated 95% HDP CrI for each treatment at **Week 16**~~each visit~~ will be reported**, together with**~~. In addition,~~ the adjusted mean difference from placebo and the associated 95% HDP CrI for each active dose at each visit ~~will also be reported together with~~**and** the probability that each treatment difference is less than 0%, -20%, -30%, and -50% ~~for each active dose at Week 16~~.

Model checking and diagnostic plots, including posterior density plots of the posterior samples for all parameters in the model and residual plots to evaluate the distributional assumptions underlying the model, will be produced. The assumption that data are missing at random will be evaluated by plotting the mean percentage change in PASI score against visit, by treatment group, for the subgroups of participants who completed 16 weeks of study drug compared with those who discontinued study drug before the Week 16 visit.

If model checking and diagnostic plots show a violation of the assumptions underlying the analysis, alternative statistical methods will be considered, appropriate to the type of violation observed. "…"

A further sensitivity analysis will be performed on the model with the primary estimand, in which participants who withdrew from study drug due to treatment failure (demonstrated by the participant commencing an oral agent, biological, or intermediate or high-potency topical therapy for plaque psoriasis) will have their percentage change from PASI imputed at all visits after study drug was discontinued as the maximum on-treatment value reached (ie, worst score carried forward).

If the assumption of similarity between the placebo cohorts is supported, a supplementary analysis will be performed on the percent change from baseline to Week 16 in PASI score using a dose-response model on the pooled cohorts. The log-linear, 3-parameter, and 4-parameter E_{max} models will be fitted and compared, with the best fitting model (lowest DIC) selected for use in the outputs.

The dose-response model will be fitted to the data using Bayesian techniques with noninformative priors for E_0 and E_{max} and an FUP for ED50 (3- and 4-parameter models only) and the slope parameter m (4-parameter model only). The rationale for this choice of inference is that the FUP shrinks the dose response towards a flat line throughout the dose range, therefore providing more conservative estimates of the dose-response relationship compared to maximum likelihood (Bornkamp 2014). The models will be fully described in the SAP.

Based on the selected model, the posterior mean with associated 95% HDP CrI, for the difference from placebo for each active dose will be produced for the pairwise differences between each active dose and placebo, together with the posterior mean and 95% HDP CrI of the treatment difference from placebo for each active dose and posterior probabilities that difference from placebo is less than 0, -20%, -30%, and -50%. A further sensitivity analysis will be performed on the dose response model, in which participants who withdrew from study drug due to treatment will have their Week 16 percentage change from PASI imputed as 100% after study drug was discontinued.

Section 7.6.2 (previously Section 7.8.2):

All secondary analyses will be performed either using the pooled placebo group if the assumption of similarity for the placebo cohorts is considered appropriate or using the **3**~~2~~ cohort-level placebo groups if it is not considered appropriate.

Unless otherwise specified, a~~A~~ll secondary analyses will be performed on the mITT set, excluding data collected after treatment discontinuation, without consideration of any protocol deviations. Dose will be treated as a categorical variable and no dose response modelling will be done. Comparisons of interest will be between individual EDP1815 doses and placebo. All posterior probabilities and CrI calculated will be considered as descriptive with no further adjustments for multiplicity performed. "…"

Mean **percentage** change from baseline in PASI score **at Weeks 4, 8, and 12** will be **analyzed as part of the MMRM for the primary estimand. The same statistics produced for the Week 16 time point will also be produced at Weeks 4, 8, and 12.**~~summarized by visit. A Bayesian MMRM model will be used to estimate treatment difference at Week 16 in the same manner as that described in Section 7.8.1 for the primary efficacy analysis.~~

The following secondary endpoints will be analyzed in the same manner as described for the primary analysis:

- **Mean absolute change from baseline in PASI score at Weeks 4, 8, 12, and 16**
- **Mean percentage change from baseline in LSS at Weeks 4, 8, 12, and 16**
- **Mean absolute change from baseline in LSS at Weeks 4, 8, 12, and 16**
- **Mean percentage change from baseline in PGA×BSA at Weeks 4, 8, 12, and 16**
- **Mean absolute change from baseline in PGA×BSA at Weeks 4, 8, 12, and 16**
- **Mean percentage change from baseline in DLQI score at Weeks 4, 8, 12, and 16**
- **Mean absolute change from baseline in DLQI score at Weeks 4, 8, 12, and 16**

- **Mean percentage change from baseline in mNAPSI total score at Weeks 4, 8, 12, and 16**

- **Mean absolute change from baseline in mNAPSI total score at Weeks 4, 8, 12, and 16**

~~Percentage of participants achieving PASI-50, PASI-75, PASI-90 and PASI-100 at Weeks 4, 8, 12, and 16 will be summarized by visit.~~

For the PASI-50, a Bayesian generalized linear mixed effects model with a logit link function will be fitted using data from all visits. Treatment*visit and baseline PASI score*visit interactions will be included in the model as fixed effects. Body mass index, gender, and other baseline covariates will also be considered and fitted as fixed effects if found to be significant ($p<0.05$). **Odds ratios and 95% HDP CrI** ~~Credible intervals~~ for each active dose compared to placebo at **each visit** ~~Week 16~~ will be presented.

A sensitivity analysis for the PASI-50 will also be performed, in the same manner as described above, in which participants who withdraw from study drug before Week 16 due to treatment failure will be included in the model with the PASI-50 endpoint imputed as 'not achieved' at all visits after study drug withdrawal.

Percentage of participants achieving PGA of 0 or 1 with a ≥2-point improvement and percentage of participants achieving a PGA of 0 will be **analyzed** ~~summarized by visit. Bayesian GLM will be used to estimate treatment differences~~ in the same manner as described above for ~~the~~ PASI-50 ~~endpoint~~.

For the time to first achievement of PASI-50, a Bayesian Cox proportional hazards model will be fitted with treatment and baseline PASI score as covariates. Hazard ratios and 95% HDP CrI for each active dose compared to placebo will be presented. ~~Mean change from baseline in PGA×BSA and LSS will be summarized by visit. Bayesian MMRM models will be used to estimate treatment differences at Week 16 in the same manner as that described in Section 7.8.1 for the primary efficacy analysis.~~

Section 7.6.3 (previously Section 7.8.3):

Exploratory endpoints will be summarized using the mITT population, with data collected after discontinuation of treatment excluded but without consideration of any protocol

deviations. **Details of all analyses to be performed on the exploratory endpoints will be detailed in the SAP** ~~No inferential analyses will be performed on the exploratory endpoints~~.

Section 7.6.7 (previously Section 7.8.7):

An interim analysis may be undertaken during the conduct of the study after at least 50% of participants have completed at least 12 weeks of treatment or withdrawn from treatment. The purpose of this analyses will be to aid in the planning of future studies and for a better understanding of the benefit/risk profile of EDP1815~~. If the recruitment is such that the full study is expected to report out before the end of 2020, this interim analysis may not be performed.~~ "..."

The interim analysis will look at the primary endpoint of percentage change from baseline in PASI score, secondary, and safety endpoints. The posterior predictive probability (Spiegelhalter et al 2004) of the percent change from baseline in PASI score being at least 20% lower in each active dose compared to the pooled placebo ~~group~~ will also be calculated, using the estimates of treatment difference found at Week 12 using the Bayesian MMRM ~~model~~ described for the primary analysis. If the posterior predictive probabilities for all active doses are found to be <30%, then the study may be stopped for futility.

Section 8.1:

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the participants treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include diaries, laboratory reports, ECG strips, etc. Electronic devices **will be used for the administration of investigator and participant responses to Clinical Outcome Assessments. Data collected via these devices will be uploaded directly to a central database for storage and analysis** ~~for administering questionnaires will upload data directly to the clinical database~~. Details will be provided in the study manual.

Section 11.3.1:

The study will be **halted**~~terminated~~ if any of the following occur:

- One death considered definitely, probably, or possibly related to the study drug

- Two or more **participants**~~subjects~~ with an SAE considered definitely, probably, or possibly related to the study drug

- Three or more **participants**~~subjects~~ with grade 3 AEs of the same type considered definitely, probably, or possibly related to the study drug

Section 12:

Bornkamp B. Practical considerations for using functional uniform prior distributions for dose-response estimation in clinical trials. Biom J. 2014;56(6):947-62.

Protocol Amendment 3.1 Hungary Specific – Summary of Major Changes

The protocol was amended to clarify the language around study drug discontinuations or study withdrawals in Section 4.2 as per request from the National Institute of Pharmacy and Nutrition (ie, Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet).

Changes have been marked as follows: new text as **bold** and deleted text as ~~strikethrough~~. Minor grammatical and formatting changes were made for clarification purposes only.

A participant ~~may~~ **will be** discontinue**d** from the study drug or withdraw**n** from the study for any of the following reasons:

~~1. The participant does not meet the protocol inclusion or exclusion criteria.~~

~~2. The participant is noncompliant with the protocol.~~

~~3.~~**1.** The participant experiences treatment failure, demonstrated by the participant commencing an oral agent, biological, or intermediate or high-potency topical therapy ~~for plaque psoriasis~~.

~~4.~~**2.** The participant has a serious or intolerable AE that in the investigator's opinion requires discontinuation from study treatment or withdrawal from the study.

~~5. The participant has laboratory safety results that reveal clinically significant hematological or biochemical changes from the baseline values.~~

~~6.~~**3.** The participant has symptoms or an intercurrent illness not consistent with the protocol requirements or that justif~~y~~**ies** withdrawal.

~~7.~~**4.** The participant is lost to follow-up.

~~8.~~**5.** Other reasons (eg, pregnancy, development of contraindications **to**~~of~~ use of study drug).

~~9.~~**6.** The participant withdraws consent, or the investigator or sponsor decides to discontinue the participant's participation in the study.

A participant may **be** discontinue**d** from the study drug or withdraw**n** from the study for any of the following reasons:

~~1. The participant does not meet the protocol inclusion or exclusion criteria.~~

~~2.~~**1.** The participant is noncompliant with the protocol.

~~3. The participant experiences treatment failure, demonstrated by the participant commencing an oral agent, biological, or intermediate or high-potency topical therapy for plaque psoriasis.~~

~~4. The participant has a serious or intolerable AE that in the investigator's opinion requires discontinuation from study treatment or withdrawal from the study.~~

~~5.~~**2.** The participant has laboratory safety results that reveal clinically significant hematological or biochemical changes from the baseline values.

~~6. The participant has symptoms or an intercurrent illness not consistent with the protocol requirements or that justify withdrawal.~~

~~7. The participant is lost to follow-up.~~

~~8. Other reasons (eg, pregnancy, development of contraindications of use of study drug).~~

~~9. The participant withdraws consent, or the investigator or sponsor decides to discontinue the participant's participation in the study.~~

3. If the participant is required to start therapy for a concurrent condition that may affect the study endpoints, eg, a disease-modifying agent for psoriatic arthritis.

In all of these instances, if the participant is to remain in the study, then the investigator should confirm that the participant is suitable to continue in the study with the medical monitor.

Protocol Amendment 4 – Summary of Major Changes

The study has been amended to include local Amendment 3.1 (Hungary) and to extend post-treatment follow-up for a maximum of up to 6 months; to add one secondary and one exploratory objective; to add definitions of response, relapse, and rebound based on PASI score; to update statistical analyses, endpoints, and supportive analyses; to add skin plaque biopsy description; to add instructions for participants on withholding emollients or moisturizers; to add clarification and remove Vitamin D and analogues from exclusion criterion #8 and add clarification to exclusion criterion #21; to clarify pre- and probiotic use; to update allowed and prohibited vaccines; to clarify that eligibility confirmation at Baseline/Visit 2 will be based on screening laboratory results; to clarify maximum dose (overdose management); to add clarification on blinding; to change 'on the morning of the visit' ECGs and vital signs to 'on the day of the visit' in footnotes of the Schedule of Assessments (SoA); to update the ideal size of lesion area for digital photography.

Administrative and minor grammatical, editorial, and formatting changes were made for clarification purposes only.

The major changes listed above have been made in addition to the edits in the following sections (and the corresponding text in the Protocol Synopsis).

Changes have been marked as follows: new text as **bold** and deleted text as ~~strikethrough~~.

Section 2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To evaluate the efficacy dose response of EDP1815 at Week 16
- To evaluate the maximal clinical benefit of EDP1815 at Week 16
- To evaluate the optimal dose of EDP1815 based on efficacy and safety up to Week 16
- To evaluate the safety and tolerability of EDP1815 (all dose levels) throughout the study

- **To evaluate relapse and rebound of plaque psoriasis after cessation of EDP1815**

Section 2.3 Exploratory Objectives

The exploratory objectives of this study are the following:

- To evaluate the time to onset of clinical response to EDP1815
- To evaluate the effect of EDP1815 treatment on patient-reported outcomes including quality of life and pain
- **To evaluate the duration of remission, treatment success, and therapeutic effect of EDP1815**
- To evaluate the effect of EDP1815 treatment on biomarkers in blood
- To evaluate the effect of EDP1815 treatment on biomarkers in skin plaques
- To evaluate the effect of EDP1815 treatment on fecal microbiome composition

Section 3.1 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-cohort, dose-ranging study of participants with mild to moderate plaque psoriasis (Section 4.1)**.**

Part A of the study comprises a screening period of up to 4 weeks, a baseline visit, a treatment period of 16 weeks (8 planned study site visits), and a **follow-up visit at Week 20 (4 weeks after cessation of dosing). Part A of the study therefore comprises a total of 11 scheduled study visits, and on completion of Part A, the primary analysis will be performed.**

Part B of the study is designed to assess the durability of treatment response and incidence of rebound of psoriasis following cessation of dosing. All participants will attend for skin assessments at Weeks 24 and 28, unless they have previously experienced treatment failure and/or had rebound of disease. A final visit at Week 40 will also be performed for those participants who experienced treatment response at

Week 16 of treatment, but have not yet met the definition of disease relapse. Part B of the study therefore comprises a maximum of 3 additional scheduled study visits with a follow-up of up to 40 weeks (24 weeks after cessation of dosing), and on completion of Part B, the final analysis will be performed. ~~period of 4 weeks (1 planned study site visit at EOS). There are a total of 11 scheduled study visits~~**.**

The study design is presented in Figure 3-1, and the SoA is presented in Table 6-1 **for Part A, and in Table 6-2 for Part B**.

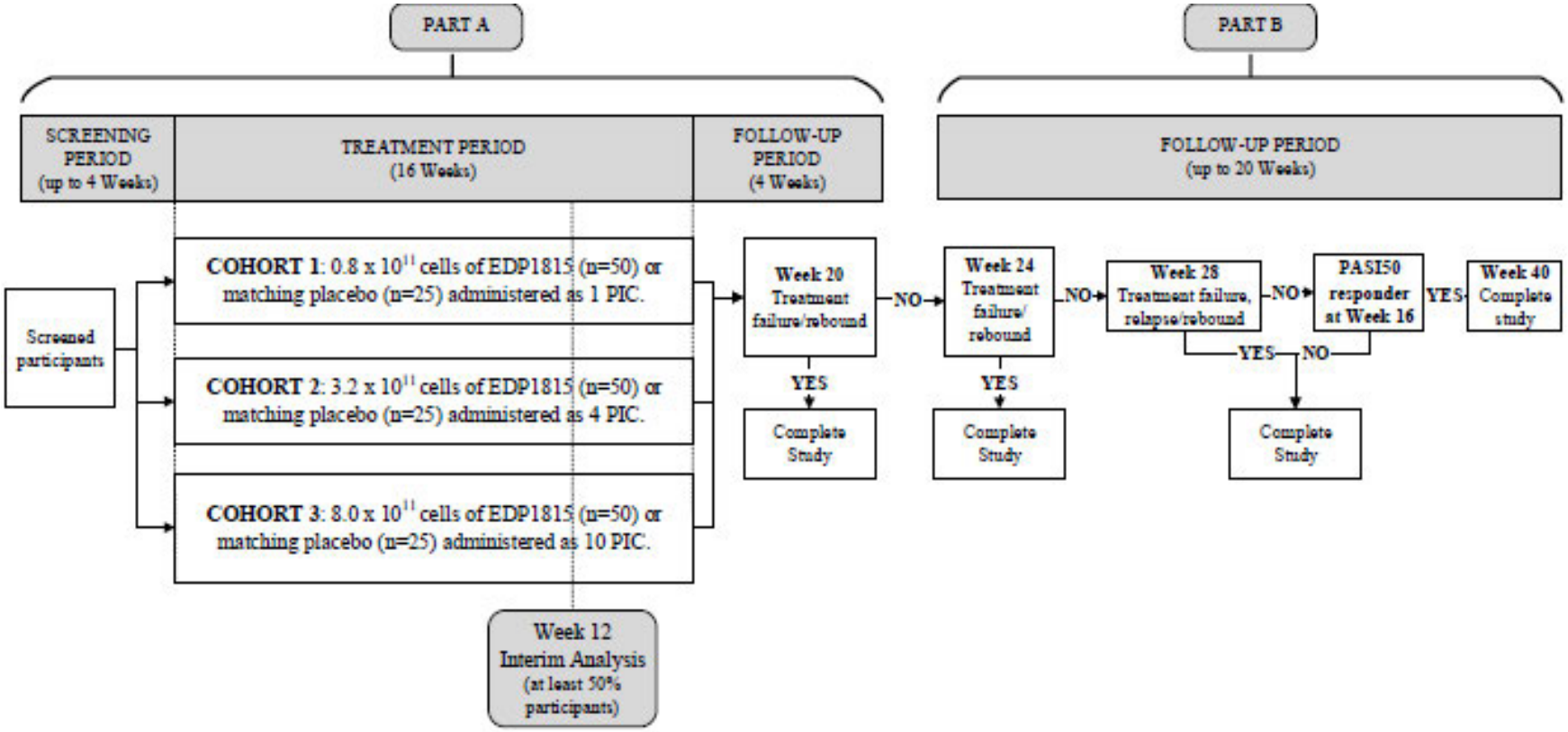
Three paragraphs without changes

After the planned 16 weeks of treatment, all participants will **have an initial follow-up visit at Week 20 (ie, 4 weeks post last dose of study treatment), completing Part A of the study; and enter Part B with continued follow-up for a maximum of 20 additional weeks (up to Week 40). The duration of follow up will depend on the initial response to study therapy and any relapse or rebound experienced after cessation of study treatment.** ~~enter a 4-week post-treatment follow-up period and undergo end of treatment evaluations.~~

The maximum planned duration **of study participation**~~for each participant~~ will be ~~24~~ **44** weeks, and the duration of the study is defined for each participant as the date signed written informed consent is provided through ~~the~~**to their** last follow-up visit. Participants will be considered to have completed the study ~~with~~ **after** the completion of all **required visits.**~~phases of the study, culminating with their EOS follow-up visit.~~

Figure 3-1 Study Design

Figure 3-1 Study Design



Note: All dosing is once daily.

Section 3.1.1 Rationale for Study Design

Added the following as last paragraph of this subsection:

Part B of the study, which includes additional visits at Weeks 24, 28, and 40, is designed to help understand the durability of treatment effect, including time to relapse and incidence of any rebound of psoriasis after treatment has completed. These are important aspects to understand regarding a psoriasis therapy (EMA guideline CHMP/EWP/2454/02, 2004).

Section 4.1 Selection of Study Population

Countries updated in the first paragraph:

Approximately 225 participants will be **randomized** ~~enrolled (randomly assigned to treatment)~~ in multiple countries, including (but not limited to) sites in the United States, the United Kingdom, ~~and~~ Poland**, and Hungary**. Participants will be assigned to study treatment only if they meet all inclusion criteria and no exclusion criteria during screening.

Section 4.1.2 Exclusion Criteria

8. Have received phototherapy or any systemic medications/treatments that could affect psoriasis or PGA evaluation (including, but not limited to oral or injectable corticosteroids, retinoids, ~~1,25-dihydroxy vitamin D3 and analogues,~~ psoralens, sulfasalazine, hydroxyurea, or fumaric acid derivatives) within 4 weeks of first administration of study drug. **This includes therapeutic doses of non-steroidal anti-inflammatory drugs such as ibuprofen, although intermittent as required use as an analgesic is permitted when required. Chronic use of low dose aspirin for cardiovascular protection is permitted.**

Exclusion criteria 9 to 13 without changes:

14. Have received live or live-attenuated **replicating** vaccin~~ation~~ within 6 weeks prior to screening or intend to have such a vaccination during the study.

Exclusion criteria 15 to 20 without changes:

21. Current acute or chronic inflammatory disease other than psoriasis or psoriatic arthritis (eg, inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus). **If a subject is off all treatment and is disease and has been symptom free for greater than 12 months, then the inflammatory disease is considered to be in remission and they may be enrolled.**

Exclusion criteria 22 to 27 without changes:

28. Initiating any OTC or prescription medication including vitamins, herbal supplements and nutraceuticals (eg, supplements including high doses of probiotics and prebiotics as usually found in capsules/tablets/powders), except acetaminophen/paracetamol and anti-histamines, within 14 days prior to baseline or anticipates change in dosage for the duration of the study period.
    Note**: P**robiotic and prebiotic foods that contain low doses are allowed (eg, yoghurt, kefir, kombuca)~~,~~**. however, supplements containing high doses of probiotics and prebiotics are not allowed at any point during the study.**

Section 4.2 Discontinuation From Study Treatment and/or Withdrawal From the Study

Clarified 3rd bullet:

- Early withdrawal from the study is defined as failing to complete the **required follow-up period**~~visit scheduled for Week 20~~.

Section 4.2.2 Withdrawal From the Study

Last paragraph updated:

Participants who withdraw from the study **during Part A** should complete the **final** assessments **listed under the Follow-up Visit (Week 20) at an unscheduled** ~~for the~~ follow-up visit, as detailed in the SoA (Table 6-1). **Participants who withdraw from the study during Part B should complete the final assessments at the Early Withdrawal Visit, as detailed in Table 6-2.**

Section 5.4.1 and 5.4.2

*Replaced '~~study manual~~' with '***IMP handling manual***'*

Section 5.5 Overdose Management

First paragraph:

An overdose is any dose of study treatment given to a participant or taken by a participant that exceeds the **maximum** dose described in the protocol **(10 capsules per day)**.

Section 5.6 Blinding

Added last paragraph:

The data will be unblinded and the primary analysis will be performed once all participants have completed 4 weeks of post-treatment follow-up at Visit 11 (Week 20; at the end of Part A). Study site staff, participants, and clinical monitors who will be involved in the collection and review of individual study data will remain blinded until Part B is completed.

Section 5.8.2 Concomitant Therapy

Second paragraph:

Non-live **and non-replicating** vaccines are permitted in this study.

Section 5.8.2.1 Prohibited Concomitant Therapy

Last paragraph:

Live or live-attenuated **replicating** vaccines are contra-indicated in this study.

Section 6 Study Assessments and Procedures

Before performing any study procedures, all potential participants will sign an ICF. Additional procedural details related to the ICF are provided in Section 9.3.

The SoA is presented in Table 6-1. Detailed instructions for study site activities will be provided in the **appropriate specific user manual**~~study manual~~**, where applicable**. High level descriptions of the study assessments are presented in the subsections of Section 6. In exceptional circumstances, study assessments may be conducted remotely (ie, at a participant's home), except for **screening,** baseline, Visit 9, and Visit 10. Remote visits can only occur if operationally possible.

*Table 6-1 Schedule of **Assessments** ~~Study Site Activities~~*

The title of this Table 6-1 was updated to 'Schedule of Assessments' as per protocol template.

*Updated and clarified **footnote a** on final assessments for participant who withdraw during Part A of this study.*

*Added **footnote b**, to add reference to the added Schedule of Post-Treatment Follow-up Assessments – Part B in Table 6-2.*

*Added text to **footnote c** (previously footnote b) to clarify that the laboratory results for eligibility confirmation (ie, at Baseline/Visit 2) will be the results from laboratory tests performed at the Screening Visit 1.*

Replaced the word '~~morning~~*' with '***day***' in **footnotes h and i** (previous footnotes g and h) and updated all other footnote letters (after the addition of new footnote b).*

*Updated and clarified text on skin plaque biopsies in **footnote k** (previous footnote j) to match the added new Section 6.1.10 (as described separately further below).*

*Updated ideal size for lesion area in **footnote l** (previous footnote k) to '***ideally greater than 2 cm by 2 cm***'.*

*Added text to clarify withholding emollients or moisturizers, at the end of **footnote n** (previous footnote m):* **Participants will be asked to withhold all emollients or moisturizers on the day of these study visits until all study assessments are completed.**

Table 6-1 Schedule of Assessments ~~Study Site Activities~~ – Part A

Procedure	**Screening**	**Baseline**	**Treatment Period**								**Follow-up[a, b]**
Day	**-28 to -7**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**85**	**113**	**141**
Week	**-4**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**20**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Visit window (days)	**--**	**--**	**5-11**	**12-18**	**19-25**	**26-32**	**40-46**	**54-60**	**82-88**	**110-116**	**134-148**
Informed consent	X										
Inclusion and exclusion criteria	X	X [cb]									
Demography	X										
HbsAg, HCV and HIV screening	X										
HLA sample [de]		X									
Medical history and current medical conditions (including duration of psoriasis)	X	X									
Full physical examination (height only at screening) [ed]	X	X	X			X			X	X	X
Pregnancy test [fe]	X	X								X	X
Laboratory assessments (hematology, serum biochemistry and CRP, and urinalysis)	X	X				X		X	X	X	X
Fasting [gf] blood sampling		X						X		X	
12-lead ECG [hg]	X	X				X				X	X
Vital signs [ih]	X	X	X	X	X	X	X	X	X	X	X
Randomization		X									
Dosing [ji]		X	X	X	X	X	X	X	X	X	
Dispense study drug		X	X	X	X	X	X	X	X		
Collect/count unused study drug			X	X	X	X	X	X	X	X	
Skin plaque biopsies [kj]		X								X	

Procedure	**Screening**	**Baseline**	**Treatment Period**								**Follow-up[a, b]**
Day	**-28 to -7**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**85**	**113**	**141**
Week	**-4**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**20**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Visit window (days)	**--**	**--**	**5-11**	**12-18**	**19-25**	**26-32**	**40-46**	**54-60**	**82-88**	**110-116**	**134-148**
Digital photography of lesion sites [lk]		X				X		X		X	X
Stool samples for microbiome investigation [mk]		X								X	X
Dispense stool diary	X										
Collect/record stool diary		X									
Blood sample for detection of systemic EDP1815		X								X	
Samples for blood biomarkers		X								X	
BSA involvement (%), PGA, PASI [nm, on]	X	X	X	X		X		X	X	X	X
LSS, mNAPSI [nm]		X	X	X		X		X	X	X	X
PSI, DLQI, PA-VAS, SF-36 (vitality and pain), Fatigue [po]		X	X	X		X		X	X	X	X
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X
Dispense dosing diary		X	X	X	X	X	X	X	X		
Collect/review dosing diary [qp]			X	X	X	X	X	X	X	X	

[a] Participants who withdraw from the study **during Part A**~~early~~ should complete the~~se~~ **final** assessments **listed under the Follow-up Visit (Week 20), at an unscheduled follow-up visit. Where relevant and when possible, this should be arranged within 72 hours of the start of a new psoriasis treatment**. In the event of early withdrawal from the study, unused study drug is to be collected/counted at this visit.

[b] **All participants will attend additional follow-up Visits 12 and 13 (see Table 6-2), unless they are considered a 'treatment failure' or meet the criteria for rebound.**

[c~~b~~] Recheck inclusion/exclusion criteria **at Baseline,** before first dose of study drug. **Screening laboratory results will be used to confirm eligibility at Baseline.**

[d~~c~~] Predose optional genetic samples.

[c]~~[d]~~ BMI will be calculated from the height and weight.

[f]~~[e]~~ Women of child-bearing potential only. Serum HCG at screening, urine thereafter. Pregnancy testing will be performed at the visits indicated or if a menstrual cycle is missed or if pregnancy is otherwise suspected.

[g]~~[f]~~ Participants will fast for at least 8 hours before glucose and lipid blood sampling

[h]~~[g]~~ A single ECG tracing is to be obtained on the ~~morning~~**day** of the visit. If, in the opinion of the investigator, there appear to be clinically significant findings, a second tracing should be obtained during the visit.

[i]~~[h]~~ Blood pressure, pulse, respiratory rate, and temperature are to be checked on the ~~morning~~**day** of the visit.

[j]~~[i]~~ The first dose will be given at the baseline visit, following random assignment to treatment. Subsequent doses are to be taken (away from the study site) once daily in the morning at approximately the same time ±2 hours. Participants should refrain from consuming acidic drinks 1 hour either side of dosing and from eating 2 hours before dosing and 1 hour after dosing. On days of study site visits during the treatment period (Visit 3 through Visit 10, inclusive), participants may dose at home.

[k]~~[j]~~ Skin plaque biopsies **(ie, a 4 mm punch biopsy, performed pre-dose by a suitably trained study personnel and processed as per laboratory manual) are to be performed after all other assessments have been completed at the end of Visits 2 and 10.** ~~are to be taken after all other assessments at visit have been completed in participating participants. A -7 day window is allowed at baseline and a +7 day window at Week 16 to accommodate availability of the dermatologist.~~

[l]~~[k]~~ Digital photographs should be taken of up to 6 lesion sites that have a lesion area **ideally greater than ≥**2 **cm by** ~~x~~ 2 cm at baseline. The same locations photographed at baseline should be followed throughout the study for each participant.

[m]~~[l]~~ Stool samples are to be collected within the 48 hours preceding each visit of stool sample collection.

[n]~~[m]~~ Investigator rating scales. **Participants will be asked to withhold all emollients or moisturizers on the day of these study visits until all study assessments are completed.**

[o]~~[n]~~ Inclusion criterion #4 (mild to moderate plaque psoriasis with plaque covering BSA of ≥3% and ≤10%, PASI score of ≥6 and ≤15, and PGA score of 2 or 3) should be reconfirmed at the baseline visit prior to randomization.

[p]~~[o]~~ Participant-reported assessments.

[q]~~[p]~~ Study staff will review the dosing diaries with participants at each visit when diaries are collected. Diaries will be reviewed for completeness and accuracy, and participants will be coached as needed on compliance with the protocol.

Table 6-2 Schedule of Post-Treatment Follow-Up Assessments – Part B

Table 6-2 was added in its entirety:

Table 6-2 Schedule of Post-Treatment Follow-Up Assessments – Part B

Procedure	**Post-Treatment Follow-Up – Part B** [a]			
Visit number	**12** [b]	**13** [b]	**14** [c]	**Early Withdrawal Visit** [a]
Months (after the End of Treatment)	**2**	**3**	**6**	
Weeks	**24**	**28**	**40**	
Day	**169**	**197**	**218**	**–**
Visit window (days)	**162-176**	**190-204**	**204-232**	**–**
BSA involvement (%), PGA, PASI [d]	X	X	X	X
LSS, mNAPSI [d]	X	X	X	X
PSI, DLQI [e]	X	X	X	X
Concomitant medication review	X	X	X	X

[a] Participants who withdraw from the study during Part B should complete the final assessments at the Early Withdrawal Visit (where relevant and when possible, this should be arranged within 72 hours of the start of a new psoriasis treatment).

[b] All participants will attend Visits 12 and 13, unless they are considered a 'treatment failure' or meet the criteria for rebound.

[c] Only participants who are classified as responders at Week 16 (Visit 10) and have not relapsed at Week 28 (Visit 13) will be eligible for Visit 14 (Week 40).

[d] Investigator rating scales. Participants will be asked to withhold all emollients or moisturizers on the day of study visits until all study assessments are completed.

[e] Participant-reported assessments.

During the screening period, participants will be advised to monitor their psoriasis symptoms and remain on a stable regimen of topical emollients and low-dose topical corticosteroid medications (if they are already taking any). **Participants will be asked to withhold the application of any emollients or moisturizers on the day of any site visit until after all the study assessments have been performed.** As part of the screening, PASI, BSA involvement, and PGA scores will be measured (inclusion criterion #4, Section 4.1.1).

Section 6.1.1 Psoriasis Area and Severity Index Score

The PASI score will be assessed as described by Langley and Ellis (2004). The PASI is a physician assessment that combines the assessment of the severity of and area affected by psoriasis into a single score in the range 0 (no disease) to 72 (maximal disease). The absolute PASI score in this study is used as part of inclusion criterion #4. The PASI percentage response rates are efficacy endpoints (ie, PASI-50, PASI-75, PASI-90, and PASI-100). For example, the percentage of participants who achieve a 75% or greater reduction in PASI score from baseline is represented by the PASI-75 value. Details of the PASI assessment will be provided in the **relevant training material.** ~~study manual~~

The below Response Definitions were added in their entirety:

Response Definitions based on PASI score at Week 16:

- **Responders:** Participants on treatment achieving PASI-50 or greater at week 16 visit
- **Relapse:** Increase in PASI score to baseline value or greater, or participant begins a new treatment for psoriasis
- **Partial Relapse:** Loss of PASI-50 response after cessation of study treatment
- **Rebound:** Increase in PASI score to 125% of baseline value or above, or onset of new pustular/erythrodermic psoriasis within 3 months of cessation of study treatment
- **Duration of remission:** Time from first achievement of PASI-100 to loss of PASI-100
- **Duration of treatment success:** Time from first achievement of PASI-50 to loss of PASI-50
- **Duration of therapeutic effect:** Time from cessation of study treatment until increase of PASI to 50% of maximum improvement from baseline

Section 6.1.4 Percent of Body Surface Area Involvement

First paragraph:

The percent of BSA involvement will be estimated for each participant, where 1% is approximately the area of the participant's handprint (Walsh et al 2013). Details of the BSA assessment will be provided in the **relevant training material**~~study manual.~~

Section 6.1.5 Modified Nail Psoriasis Severity Index

First paragraph:

The mNAPSI is a numeric, reproducible, objective, and simple tool for physicians to evaluate the severity of nail bed psoriasis and nail matrix psoriasis by area of involvement in the nail unit (Cassell et al 2007). Details of conducting the mNAPSI will be provided in the **relevant training material**~~study manual~~.

Section 6.1.6, 6.1.8, and 6.1.9

Deleted the last sentence in all three subsections

Section 6.1.7 Psoriasis Symptom Inventory

The PSI is a patient reported outcomes instrument that is used to assess the severity of plaque psoriasis symptoms (Bushnell et al 2013). All symptoms (itch, redness, scaling, burning, cracking, stinging, flaking, and pain) are rated on a 5-point severity scale. The PSI demonstrated good construct validity and was sensitive to within-subject change ($p<0.0001$). Details of administering the PSI will be provided in the **specific user manual**~~study manual~~.

Section 6.1.10 Biopsy of Skin Plaque (this subsection was added in its entirety)

Skin plaque biopsies (ie, a 4 mm punch biopsy, performed pre-dose by a suitably trained study personnel and processed as per laboratory manual) are to be performed after all other assessments have been completed at the end of Visits 2 and 10.

Section 6.2.1.2 Eliciting and Documenting Adverse Events

Adverse events will be reported from the date of signed informed consent and **through for 28 days after the cessation of dosing. Adverse events occurring after the 28 days post-treatment would only be reported if the investigator considers it to be related to the study treatment.**~~through the final follow-up visit.~~

Section 6.2.1.3 Reporting Adverse Events

Added the following two bullets:

- **Investigator-specific assessment if the AE is related to a recent/current COVID infection**
- **If a COVID positive PCR test received within last 14 days**

Section 6.4 Laboratory Analyses

Last paragraph

All protocol-required laboratory assessments, as defined in this section, must be conducted in accordance with the laboratory manual and the SoA (Table 6-1). **Screening laboratory results will be used to confirm eligibility at Baseline (Visit 2).** If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the

investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

Section 6.4.3 Pharmacodynamics and Biomarkers

Procedures for sample collection, processing, storage, and shipment will be detailed in the study **specific laboratory** manual. Biomarkers are exploratory endpoints and analytical results for biomarkers will not be included in the CSR. They will be reported separately from the CSR.

Digital photographs should be taken of up to 6 lesion sites that have a lesion area **ideally greater than** ≥2 **cm by** ~~×~~ 2 cm at baseline. The same locations photographed at baseline should be followed throughout the study for each participant. Procedural details for digital photography will be provided in the **specific user manual**~~study manual~~.

Section 6.4.3.1 Histologic Assessment

A 4 mm punch biopsy will be taken by suitably trained study personnel (see Section 6.1.10). Standard histology will be performed on skin plaque biopsies (including epidermal thickness, basal mitotic counts and immune cell infiltrates, immunohistochemistry) from approximately 15 participants in each cohort. Details will be provided in the study **specific laboratory** manual. The histologic evaluations are exploratory and are outside the scope of the CSR.

Section 7 Statistical Considerations

Added as last paragraph:

The primary analysis for the study will occur after all participants have completed 4 weeks of follow-up after their last dose of study medication (end of Part A). The final analysis for the study will occur when all participants have completed the required relapse and rebound follow-up period of up to 24 weeks post-treatment (end of Part B).

Section 7.1.1 Primary Efficacy Estimand

Added after first paragraph:

For the primary analysis, **3** ~~2~~ supportive estimands will also be considered:

- To assess the impact of intercurrent events related to protocol deviations believed to impact efficacy, a supportive analysis will be performed where all data collected after any such identified protocol deviations will be excluded. Participants who had a protocol deviation believed to impact efficacy prior to the first dose of treatment (hypothetical strategy based on adherence to treatment and the aspects of the protocol which impact efficacy) will be completely excluded from this analysis.

- To assess the impact of treatment discontinuation **for any reason**, a supportive analysis will be performed in which all data collected ~~during~~ **up to** the ~~study~~**end of Week 16**, including any data collected after treatment discontinuation will be included (treatment policy strategy).

- **To assess the impact of treatment discontinuation due to a requirement for alternative therapy, a supportive analysis will be performed where the highest PASI score recorded prior to treatment discontinuation will be applied to all expected visits after treatment discontinuation up to Week 16.**

The primary analysis will be performed using a Bayesian MMRM as fully described in Section 7.6.1. Data from visits prior to Week 16 will be included in the model and missing data will not be explicitly imputed.

Supportive analyses will also be performed in the same manner, using the ~~2 alternative~~ **3 supportive** estimands as defined above. These will explore the possible impact of the intercurrent events of treatment discontinuation **for any reason, treatment discontinuation due to requirement for alternative treatment,** and events relating to protocol deviations that may have an impact on efficacy.

Table 7-1 Summary of Secondary Estimands

*Added the following **3 rows** as last rows of this table:*

Population of interest	Endpoint	Consideration of intercurrent events	Summary measure
mITT set	Mean absolute change from baseline in mNAPSI total score at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active dose and pooled placebo at each visit
Week 16 responders set	Cumulative incidence of partial relapse at Weeks 20, 24, 28, and 40	To include all data collected after treatment discontinuation	Proportion of participants to relapse in each treatment group at each visit
Week 16 responders set	Cumulative incidence of complete relapse at Weeks 20, 24, 28 and 40	To include all data collected after treatment discontinuation	Proportion of participants to relapse in each treatment group at each visit
mITT set	Cumulative incidence of rebound at Weeks 20, 24, 28 and 40	To include all data collected after treatment discontinuation	Proportion of participants to rebound in each treatment group at each visit

Section 7.2 Exploratory Endpoints

The exploratory endpoints include the following:

- Percentage of participants achieving PASI-50, PASI-75, PASI-90, and PASI-100 at Weeks 4, 8, and 12
- Percentage of participants achieving PGA of 0 or 1 with a ≥2-point improvement at Weeks 4, 8, and 12
- Percentage of participants achieving PGA of 0 at Weeks 4, 8, and 12
- Mean change from baseline in PSI quality of life **total and itch** scores at Weeks 12 and 16
- Mean percentage change from baseline in PSI quality of life **total and itch** scores at Weeks 12 and 16
- Mean change from baseline in Pain and Fatigue scores at Weeks 4, 8, 12, and 16

- Mean percentage change from baseline in Pain and Fatigue scores at Weeks 4, 8, 12, and 16
- Mean change from baseline in fasting blood glucose and fasting lipid panel at Weeks 8 and 16
- **Mean duration of remission in participants who achieve PASI-100**
- **Mean duration of treatment success in participants who achieve PASI-50**
- **Mean duration of therapeutic response in participants after cessation of study treatment**

Section 7.4 Analysis Sets

Added definition for Week 16 Responders Set after PPS definition:

Week 16 responders set: The Week 16 responders set will consist of all mITT participants who achieved a PASI-50 response at Week 16.

Table 7-2 Deviations with a Potential Impact on Efficacy

Description	Evaluation Period	Impact on PPS analyses
Not meeting inclusion criteria 3, 4, or 6 or meeting any of exclusion criteria 1-12 or 27	Baseline	Exclude participant from PPS.
Use of any prohibited medication (Section 5.8.2.1)	Throughout study	If start date of prohibited medication ≤ date of first dose of study drug then exclude participant from PPS. Otherwise, include participant in PPS but exclude all data collected on or after start date of prohibited medication.

Description	Evaluation Period	Impact on PPS analyses
Compliance with study drug <80%	Evaluated in 4**8**-week periods (Weeks 1-**8,**~~4, 5-8, 9-12and 13~~ **9**-16)	If participant is non-compliant within Week 1-**8**~~4~~ treatment period, then exclude from PPS. **If participant is non-compliant only within Week 9-16 treatment period**~~Otherwise~~, include participant in PPS but exclude all data collected after the **Week 8 visit date.** ~~start of the first non-compliant 4-week period.~~ ~~The 4-weekly treatment periods will be defined by the occurrence of the Week 4, 8, 12, and 16 visits (eg, Week 5-8 compliance will look at compliance from the day after the Week 4 visit to the day of the). If visits are missed completely without withdrawal from the study, then the visit date will be approximated using the middle of the neighboring attended visits.~~
More than 7 consecutive days with no study medication without participant being permanently withdrawn from study medication	**Throughout study**	**Participant will not be excluded from PPS, but all data collected after the 8th consecutive day with no study medication will be excluded.**
More than 14 total days with no study medication (does not need to be continuous)	**Throughout study**	**Exclude participant from PPS.**

Section 7.5 Description of Subgroups to be Analyzed

~~No subgroup analyses are planned, but~~ **R**esults may be summarized by individual cohort.

Subgroup analysis of the primary estimand will be performed based on the following subgroups:

- **Baseline PASI score (<10, ≥10)**
- **Baseline PGA score (2, 3)**
- **Baseline BMI (<30kg/m^2, ≥30kg/m^2)**

Section 7.6.1 Analysis of Primary Efficacy Endpoint

First paragraphs:

The assumption that the 3 cohorts of placebo participants can be pooled into a single placebo group to be used as a control for all active doses will be examined using mean (±SD) plots **and box plots** of percent change in PASI score against time. **In addition, a mixed model for repeated measures (MMRM) will be used to compare the 3 cohorts of placebo participants. The model will include parameters for cohort, visit and baseline PASI score together with cohort*visit and baseline PASI score*visit interactions. LS mean (95% CI) estimates for each placebo cohort will be plotted by visit.**

A decision will be made by the Evelo study team**, based** on **examination of the above figures and model,** on whether the pooling strategy is appropriate.

The primary analysis will be performed using a Bayesian MMRM. The model will include parameters for treatment*visit and baseline PASI score*visit interactions. Body mass index, gender, **country,** and **time since diagnosis**~~other baseline covariates~~ will also be considered and included as parameters if found to be significant ($p<0.05$). The model will not include an intercept. Visit will consist of 6 levels (Weeks 1, 2, 4, 8, 12, and 16) and treatment will consist of 4 levels (pooled placebo, EDP1815 0.8×10^{11} cells, EDP1815 3.2×10^{11} cells, and EDP1815 8.0×10^{11} cells) if the placebo pooling strategy is considered appropriate or 6 levels (Placebo matching EDP1815 0.8×10^{11} cells, Placebo matching EDP1815 3.2×10^{11} cells, Placebo matching EDP1815 8.0×10^{11} cells, EDP1815 0.8×10^{11} cells, EDP1815 3.2×10^{11} cells, and EDP1815 8.0×10^{11} cells) if the placebo pooling strategy is not considered appropriate.

Five paragraphs without changes

This primary analysis will be repeated using the ~~2~~ **3** supportive estimands defined in Section 7.1.1.

Deleted the following paragraph:

~~A further sensitivity analysis will be performed on the model with the primary estimand, in which participants who withdrew from study drug due to treatment failure (demonstrated by the participant commencing an oral agent, biological, or intermediate or high potency topical~~

~~therapy for plaque psoriasis) will have their percentage change from PASI imputed at all visits after study drug was discontinued as the maximum on-treatment value reached (ie, worst score carried forward).~~

Added as last paragraph:

All summaries and analyses defined above for the primary estimand will be repeated using the subgroups defined in Section 7.5.

Section 7.6.2 Analysis of Secondary Efficacy Endpoint

Second paragraph, last sentence:

All **p-values,** posterior probabilities**, CI,** and CrI calculated will be considered as descriptive with no further adjustments for multiplicity performed.

Added third paragraph:

The covariates selected for the Bayesian MMRM analysis for the primary estimand will also be used in all other analytical models including covariates.

Two paragraphs without changes

From fifth paragraph to end of this section:

For the PASI-50, a ~~Bayesian~~ generalized linear mixed effects model with a logit link function will be fitted using data from all visits. **Treatment, visit, and baseline PASI score terms will be included in the model as fixed effects, together with** treatment*visit and baseline PASI score*visit interactions**,** ~~will be included in the model as fixed effects. Body mass index, gender,~~ and ~~other~~ **any** baseline covariates **selected in the primary analysis model for the primary estimand.**~~will also be considered and fitted as fixed effects if found to be significant (p<0.05).~~ Odds ratios and 95% ~~HDP CrI~~**CIs** for each active dose compared to placebo at each visit will be presented.

A ~~sensitivity~~ **supportive** analysis for the PASI-50 will also be performed, in the same manner as described above, in which participants who withdraw from study drug before Week 16 due

to ~~treatment failure~~ **requirement for alternative therapy** will be included in the model with the PASI-50 endpoint imputed as 'not achieved' at all **expected** visits after study drug withdrawal.

A sensitivity analysis will also be performed on the PASI-50. Bayesian logistic regression models will be individually fitted at each of Weeks 4, 8, 12, and 16. The model will include parameters for treatment and baseline PASI score together with any baseline covariates selected in the primary analysis model for the primary estimand. The posterior odds-ratios for each pairwise comparison of an active EDP1815 dose and placebo with associated 95% HDP CrI will be presented together with the posterior probability that the true odds ratio >1.

Percentage of participants achieving PGA of 0 or 1 with a ≥2-point improvement and percentage of participants achieving a PGA of 0 will be analyzed in the same manner as described above for PASI-50 **with the exception that the sensitivity analysis using the Bayesian logistic regression model will only be fitted on the Week 16 data**.

For the time to first achievement of PASI-50, a ~~Bayesian Cox proportional hazards model~~**nonparametric survival analysis for interval censored data** will be **performed**~~fitted with treatment and baseline PASI score as covariates. Hazard ratios and 95% HDP CrI for each active dose compared to placebo will be presented~~. **The expectation-maximization iterative complex minorant (EMICM) method for iterative computation of the nonparametric maximum likelihood estimator for the survival function (Wellner and Zahn 1997) will be used. The number and proportion of participants who meet the PASI-50 at least once during the study will be presented. A generalized log-rank test will be used to compare each active dose with placebo and the p-value for treatment difference will also be presented. The estimated survival curves for each treatment group will also be presented.**

Cumulative incidence of partial relapse and complete relapse at Weeks 20, 24, 28, and 40 will be summarized by treatment group on the Week 12 responders set.

Cumulative incidence of rebound after cessation of study treatment at Weeks 20, 24, 28, and 40 will be summarized by treatment group.

Section 7.6.3 Analyses of Exploratory Efficacy Endpoints

Added as last paragraph:

A further exploratory analysis will be performed on the Week 16 results. Adjusted indirect comparisons, pivoted around placebo, will be performed against publicly available data from two studies in apremilast in mild/moderate or moderate psoriasis. Further details will be provided in the study SAP.

Section 12 References

Added the below 2 references in alphabetical order:

European Medicines Agency. Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. European Medicines Agency CHMP/EWP/2454/02 corr, 18 November 2004.

Wellner JA, Yihui Z. A hybrid algorithm for computation of the nonparametric maximum likelihood estimator from censored data. J Am Stat Assoc. 1997;92(439):945-59.

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Cohort, Dose-Ranging Study Investigating the Effect of EDP1815 in the Treatment of Mild to Moderate Plaque Psoriasis" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with Protocol Version 5.0, dated 17 November 2020, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Evelo Biosciences Inc. or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to participants. I agree to administer study treatment only to participants under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Participant identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Evelo Biosciences Inc.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

Table of Contents

List of Tables

List of Figures

Protocol Synopsis

Protocol Number:	EDP1815-201
Title:	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Cohort, Dose-Ranging Study Investigating the Effect of EDP1815 in the Treatment of Mild to Moderate Plaque Psoriasis
Sponsor:	Evelo Biosciences Inc. 620 Memorial Drive, Suite 500 Cambridge, MA 02139 USA
Study Phase:	Phase 2
Study Sites:	Multiple countries, including (but not limited to) sites in the United States, the United Kingdom, Poland, and Hungary.
Indication:	Treatment of mild to moderate plaque psoriasis
Rationale:	Evelo Biosciences Inc. (Evelo) is developing medicines based on single strains of bacteria as a new class of therapeutic agents. These therapeutic agents are human commensal organisms that offer the potential of systemic immune system modulation following oral administration, without systemic exposure. EDP1815 is a pharmaceutical preparation of a strain of *Prevotella histicola* isolated from a human duodenal biopsy: it has not been genetically modified. Studies of EDP1815 in vitro in a range of human and mouse assays and studies in vivo in model symptoms support the use of EDP1815 in the treatment of inflammatory diseases including psoriasis. Oral administration of EDP1815 to mice results in striking pharmacodynamic effects on animal models of delayed-type hypersensitivity, fluorescein isothiocyanate cutaneous hypersensitivity, collagen-induced arthritis and experimental acute encephalomyelitis. The high degree of consistency of both effect and dose suggests the potential for clinical benefit across multiple type 1, type 2, and type 3 inflammatory conditions. No potentially related adverse effects were seen in the animals used in these experiments with daily dosing for up to 3 weeks or with alternate day dosing for over 7 weeks. Immunophenotyping ex vivo in these models shows increased regulatory T cell numbers and regulatory dendritic cells in spleen and mesenteric lymph nodes, as well as decreases in pro-inflammatory cytokines such as IL-23p40, IL-17, TNFα, IL-6, and IL-13. Treatment also led to enhancement of gut intestinal barrier integrity, which is often disrupted in patients with inflammatory diseases. These effects on immune parameters have

been observed both within and outside the GI tract, which demonstrates that host-microbe interactions in the gut can affect the immune response in peripheral tissues.

Psoriasis is a chronic immune-mediated type 1/3 inflammatory skin disease in which hyperactive T cells trigger excessive keratinocyte proliferation. This results in the formation of raised erythematous plaques with scaling. Psoriatic lesions can appear anywhere on the body but are most often seen on the knees, elbows, scalp, and lumbar area. Critical events in the inflammatory process include activation of Langerhans cells and T cells, selective trafficking of activated T cells to the skin, and induction of an inflammatory cytokine and chemokine cascade in skin lesions. Clinical data have validated the role of anti-TNFα, anti-IL-17, and anti-IL-23 therapy in moderate to severe psoriasis. For patients with mild to moderate psoriasis, therapy usually involves topical agents (topical corticosteroids, vitamin D3 analogs), with topical corticosteroids providing the greatest range of efficacy and a wide range of formulations. More recently, physicians are prescribing apremilast, a first-in-class oral PDE4 inhibitor, ahead of biological therapy, which includes etanercept, infliximab, adalimumab, ustekinumab, and secukinumab.

In Evelo study EDP1815-101, a total of 56 participants have participated in Cohorts 1-4, with 36 of these participants receiving EDP1815 once daily; 16 of these were treated for 14 days (healthy volunteers) and 20 participants with psoriasis were treated for 28 days. Clinical responses, similar to apremilast and tofacitinib at the same time point, have been observed on the (psoriatic) LSS and PASI at Day 28. Furthermore, at the Day 42 follow-up visit, when participants were “off treatment” for 14 days, there was continued improvement in the pharmacodynamic response as measured by both LSS and PASI for participants administered the higher dose, but not the lower dose, suggesting a dose relationship on the durability of effect. The safety profile of EDP1815 was similar to placebo, with no SAEs or AEs of severe intensity.

The evidence available so far suggests EDP1815 is very well tolerated and it continues to undergo clinical development in mild to moderate psoriasis. A well-tolerated oral therapy could offer significant benefit in the treatment of psoriasis and it is presently anticipated that EDP1815 would be used in established but early disease, before the use of biologic therapies.

This Phase 2 study has been designed to investigate the clinical safety and efficacy of EDP1815 and to identify an optimal dose.

Objectives:

Primary Objective:

The primary objective of this study is to evaluate the safety and efficacy of 3 different doses of EDP1815 for the treatment of psoriasis following daily dosing for 16 weeks.

Secondary Objectives:

The secondary objectives of this study are the following:

- To evaluate the efficacy dose response of EDP1815 at Week 16
- To evaluate the maximal clinical benefit of EDP1815 at Week 16
- To evaluate the optimal dose of EDP1815 based on efficacy and safety up to Week 16
- To evaluate the safety and tolerability of EDP1815 (all dose levels) throughout the study
- To evaluate relapse and rebound of plaque psoriasis after cessation of EDP1815

Exploratory Objectives:

The exploratory objectives of this study are the following:

- To evaluate the time to onset of clinical response to EDP1815
- To evaluate the effect of EDP1815 treatment on patient-reported outcomes including quality of life and pain
- To evaluate the duration of remission, treatment success, and therapeutic effect of EDP1815
- To evaluate the effect of EDP1815 treatment on biomarkers in blood
- To evaluate the effect of EDP1815 treatment on biomarkers in skin plaques
- To evaluate the effect of EDP1815 treatment on fecal microbiome composition

Estimands:

Primary Estimands

The primary estimand will be the effect of EDP1815 on the percent change in PASI score from baseline to Week 16 in the mITT set of all treated participants, regardless of deviations from the protocol. Only data collected while on treatment will be used to account for the intercurrent event of treatment discontinuation (hypothetical strategy based on adherence to treatment only). The posterior mean difference between each active dose and the pooled placebo will be estimated.

For the primary analysis, 3 supportive estimands will also be considered:

- To assess the impact of intercurrent events related to protocol deviations believed to impact efficacy, a supportive analysis will be performed where all data collected after any such identified protocol deviations will be excluded. Participants who had a protocol deviation believed to impact efficacy prior to the first dose of treatment (hypothetical strategy based on adherence to treatment and the aspects of the protocol which impact efficacy) will be completely excluded from this analysis.
- To assess the impact of treatment discontinuation for any reason, a supportive analysis will be performed in which all data collected up to the end of Week 16, including any data collected after treatment discontinuation will be included (treatment policy strategy).
- To assess the impact of treatment discontinuation due to a requirement for alternative therapy, a supportive analysis will be performed where the highest PASI score recorded prior to treatment discontinuation will be applied to all expected visits after treatment discontinuation up to Week 16.

The primary analysis will be performed using a Bayesian MMRM. Data from visits prior to Week 16 will be included in the model and missing data will not be explicitly imputed.

Supportive analyses will also be performed in the same manner, using the 3 supportive estimands as defined above. These will explore the possible impact of the intercurrent events of treatment discontinuation for any reason, treatment discontinuation due to requirement for alternative treatment, and events relating to protocol deviations that may have an impact on efficacy.

Summary of Secondary Estimands:

For all secondary estimands, the population of interest will be the mITT set, except for the two endpoints, which are based on the Week 16 responders analysis set.

Endpoint	Consideration of intercurrent events	Summary measure
Mean percentage change from baseline in PASI Score at Weeks 4, 8, and 12	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active treatment group and pooled placebo at each visit

Mean absolute change from baseline in PASI Score at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active treatment group and pooled placebo at each visit
Achievement of PASI-50 at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior odds ratio for response between each active treatment group and pooled placebo at each visit
Time to first achievement of PASI-50	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Hazard ratio for each active group versus placebo
Achievement of PASI-75, PASI-90 and PASI-100 at Week 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Proportion of response for each endpoint in each treatment group at each visit
Achievement of PGA of 0 or 1 with a ≥2-point improvement from baseline at Week 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior odds ratio for response between each active treatment group and pooled placebo
Achievement of PGA of 0 at Week 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior odds ratio for response between each active treatment group and pooled placebo
Mean percentage change from baseline in PGA×BSA at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active treatment group and pooled placebo at each visit
Mean absolute change from baseline in PGA×BSA at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active treatment group and pooled placebo at each visit
Mean percentage change from baseline in LSS at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active dose and pooled placebo at each visit
Mean absolute change from baseline in LSS at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active dose and pooled placebo at each visit
Mean percentage change from baseline in DLQI score at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active dose and pooled placebo at each visit
Mean absolute change from baseline in DLQI score at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active dose and pooled placebo at each visit
Mean percentage change from baseline in mNAPSI	To include all data collected prior to treatment	Posterior mean difference between each active dose

total score at Weeks 4, 8, 12, and 16	discontinuation, regardless of protocol deviations	and pooled placebo at each visit
Mean absolute change from baseline in mNAPSI total score at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active dose and pooled placebo at each visit
Week 16 responders set: Cumulative incidence of partial relapse at Weeks 20, 24, 28, and 40	To include all data collected after treatment discontinuation	Proportion of participants to relapse in each treatment group at each visit
Week 16 responders set: Cumulative incidence of complete relapse at Weeks 20, 24, 28, and 40	To include all data collected after treatment discontinuation	Proportion of participants to relapse in each treatment group at each visit
Cumulative incidence of rebound at Weeks 20, 24, 28, and 40	To include all data collected after treatment discontinuation	Proportion of participants to rebound in each treatment group at each visit

Study Population: **Inclusion Criteria**

Each participant must meet all the following criteria to be enrolled in this study:

1. Give written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements.
2. Males or females ≥18 and ≤70 years old at the time of informed consent.
3. A documented diagnosis of plaque psoriasis for ≥6 months.
4. Have mild to moderate plaque psoriasis with plaque covering BSA of ≥3% and ≤10% and meet **both** of the following additional criteria:
    a. PASI score of ≥6 and ≤15, and
    b. PGA score of 2 or 3.

    All parameters in this criterion should be reconfirmed at baseline visit prior to randomization.
5. Meet the following contraception criteria:
    a. Male participants:
        i. A male participant must agree to use contraception as detailed in Appendix 13.1 of this protocol during their participation in this study and for a period of 90 days after the last

dose and refrain from donating sperm during this period.

b. Female participants:
    i. A female participant is eligible to participate if she is not pregnant (Appendix 13.1), not breastfeeding, and at least 1 of the following conditions applies:
        1. Not a WOCBP as defined in Appendix 13.1, OR
        2. A WOCBP who agrees to follow the contraceptive guidance in Appendix 13.1 during their participation in this study, 28 days prior to the first dose and for at least 1 complete menstrual cycle (≥28 days) after the last dose.

6. Agrees to not increase their usual sun exposure during the study.

Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

1. Have received EDP1815 within the 3 months prior to screening.
2. Have a diagnosis of non-plaque psoriasis.
3. Plaque psoriasis restricted to scalp, palms and soles only.
4. Evidence of skin conditions that would interfere with psoriasis evaluation or treatment response (eg, atopic dermatitis, fungal or bacterial superinfection).
5. Having received systemic immunosuppressive therapy (MTX, apremilast, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, and tacrolimus) within 4 weeks of first administration of study drug.
6. Unresponsive to prior use of biologics (including, but not limited to, TNFα inhibitors, natalizumab, efalizumab, anakinra or agents that modulate B cells or T cells).
7. If prior biologic therapy and responsive, participants must have been off therapy for at least 12 months prior to first administration of study drug.

8. Has received phototherapy or any systemic medications/treatments that could affect psoriasis or PGA evaluation (including, but not limited to oral or injectable corticosteroids, retinoids, psoralens, sulfasalazine, hydroxyurea, or fumaric acid derivatives) within 4 weeks of first administration of study drug. This includes therapeutic doses of non-steroidal anti-inflammatory drugs such as ibuprofen, although intermittent as required use as an analgesic is permitted when required. Chronic use of low dose aspirin for cardiovascular protection is permitted.
9. Currently receiving lithium, antimalarials, leflunomide, or IM gold, or have received lithium, antimalarials, IM gold, or leflunomide within 4 weeks of first administration of study drug.
10. Have used topical medications/treatments that could affect psoriasis or PGA evaluation (including [but not limited to] high- and mid-potency corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, picrolimus, and tacrolimus) within 2 weeks of the first administration of study drug. Topical unmedicated emollients and low-potency topical corticosteroids are not excluded.
11. Gastrointestinal tract disease (eg, short-bowel syndrome, diarrhea-predominant irritable bowel syndrome) that could interfere with GI delivery and transit time.
12. Active inflammatory bowel disease.
13. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Day 1 (Visit 2).
14. Has received live or live-attenuated vaccination within 6 weeks prior to screening or intends to have such a vaccination during the study.
15. Clinically significant abnormalities in screening laboratory values that would render a participant unsuitable for inclusion (per investigator judgment).
16. For women, serum creatinine ≥125 µmol/L (1.414 mg/dL); for men, serum creatinine ≥135 µmol/L (1.527 mg/dL).
17. ALT and AST >2 × ULN.
18. Known history of or positive test for HIV, or active infection with hepatitis C or chronic hepatitis B.
19. History of clinically significant acute cardiac or cerebrovascular event within 6 months before screening

(includes stroke, transient ischemic attack, and coronary heart disease [angina pectoris, myocardial infarction, heart failure, revascularization procedures]).

20. In the opinion of the investigator, evidence of clinically important cardiac conduction abnormalities at screening as judged by ECG.
21. Current acute or chronic inflammatory disease other than psoriasis or psoriatic arthritis (eg, inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus). If a subject is off all treatment and is disease and has been symptom free for greater than 12 months, then the inflammatory disease is considered to be in remission and they may be enrolled.
22. Hypersensitivity to *P histicola* or to any of the excipients.
23. Active untreated mental or psychiatric disorder. Participants who are on stable dosing of medication for a mental or psychiatric disorder for at least 6 months before screening and whose treating physicians consider them to be mentally stable may be enrolled.
24. Any major or minor GI surgery within 6 months of screening.
25. Any major surgery within 6 months of screening.
26. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.
27. Treatment with another investigational drug, biological agent, or device within 1 month of screening, or 5 half-lives of investigational agent, whichever is longer.
28. Initiating any OTC or prescription medication including vitamins, herbal supplements and nutraceuticals (eg, supplements including high doses of probiotics and prebiotics as usually found in capsules/tablets/powders), except acetaminophen/paracetamol and anti-histamines, within 14 days prior to baseline or anticipates change in dosage for the duration of the study period. Note that probiotic and prebiotic foods that contain low doses are allowed (eg, yoghurt, kefir, kombucha).
29. Blood donation of >100 mL within 30 days of screening or of >499 mL within 12 weeks of screening.
30. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the investigator.

31. Have any other conditions, which, in the opinion of the investigator or sponsor, would make the participant unsuitable for inclusion or could interfere with the participant participating in or completing the study.

Study Design:

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-cohort, dose-ranging study of participants with mild to moderate plaque psoriasis.

Part A of the study comprises a screening period of up to 4 weeks, a baseline visit, a treatment period of 16 weeks (8 planned study site visits), and a follow-up visit at Week 20 (4 weeks after cessation of dosing). Part A of the study therefore comprises a total of 11 scheduled study visits, and on completion of Part A, the primary analysis will be performed.

Part B of the study is designed to assess the durability of treatment response and incidence of rebound of psoriasis following cessation of dosing. All participants will attend for skin assessments at Weeks 24 and 28, unless they have previously experienced treatment failure and/or had rebound of disease. A final visit at Week 40 will also be performed for those participants who experienced treatment response at Week 16 of treatment, but have not yet met the definition of disease relapse. Part B of the study therefore comprises a maximum of 3 additional scheduled study visits with a follow-up of up to 40 weeks (24 weeks after cessation of dosing), and on completion of Part B, the final analysis will be performed.

The study design is presented in Figure 3-1, and the SoA is presented in Table 6-1 for Part A, and in Table 6-2 for Part B.

After eligibility is confirmed during the screening period, participants will be randomly assigned in a 1:1:1 ratio to 1 of the following 3 parallel cohorts:

- Cohort 1: 0.8×10^{11} cells of EDP1815 or matching placebo administered as 1 PIC, once daily.
- Cohort 2: 3.2×10^{11} cells of EDP1815 or matching placebo administered as 4 PICs, once daily.
- Cohort 3: 8.0×10^{11} cells of EDP1815 or matching placebo administered as 10 PICs, once daily.

In each cohort, approximately 75 participants will be randomly assigned in a 2:1 ratio to receive either EDP1815 or matching placebo once daily for 16 weeks.

An interim analysis may be performed after at least 50% of participants have completed at least 12 weeks of treatment.

	After the planned 16 weeks of treatment, all participants will have an initial follow-up visit at Week 20 (ie, 4 weeks post last dose of study treatment), completing Part A of the study; and enter Part B with continued follow-up for a maximum of 20 additional weeks (up to Week 40). The duration of follow up will depend on the initial response to study therapy and any relapse or rebound experienced after cessation of study treatment.
Estimated Study Duration:	The maximum planned duration of study participation will be 44 weeks, and the duration of the study is defined for each participant as the date signed written informed consent is provided through to their last follow-up visit. Participants will be considered to have completed the study after the completion of all required visits.
Efficacy Assessments:	The efficacy assessments will include the PASI score, the LSS, the National Psoriasis Foundation Psoriasis Score version of a static PGA, the percent of BSA involvement, the mNAPSI, the DLQI, the PSI, the SF-36 Bodily Pain Scale, the VAS Pain assessment, the vitality subscale of the SF-36 (to assess fatigue), and a fatigue VAS.
Pharmacokinetic or Pharmacodynamic Assessments:	Pharmacokinetic assessments will be limited to a predose blood sample at baseline and another sample at the Week 16 visit (end of treatment). Pharmacodynamic and biomarker assessments are exploratory endpoints and analytical results for biomarkers will not be included in the CSR. They will be reported separately from the CSR. Pharmacodynamic and biomarker assessments include digital photography of up to 6 lesion sites, standard histologic assessments of skin plaque biopsies, mRNA transcription analysis of skin plaque biopsies, blood cytokine and chemokine analyses, and microbiome composition of the fecal microbiome.
Safety and Tolerability Assessments:	Safety and tolerability assessments include monitoring AEs (including SAEs), monitoring concomitant medications, BSFS categorization (recorded in a stool diary), physical examinations, vital sign measurements, and ECGs.
Details of Applicable Monitoring Committee:	There will be no safety review committee or data monitoring committee.
Study drug, Dosage, and Route of Administration:	The study drug will be capsules containing EDP1815 or matching capsules containing placebo. There will be 3 dosing cohorts, with dosages of 1 capsule, 4 capsules, or 10 capsules; capsules of EDP1815 each contain

8.0×10^{10} cells of EDP1815, while placebo capsules contain no bacteria.

Participants will self-administer their doses of study drug orally in the morning with water.

Sample Size:

The sample size of 225 participants in total, has been chosen to explore the tolerability and safety of EDP1815. Although the study will use a model-based probability inference approach in a Bayesian framework, the following power calculation was also performed (using a basic frequentist approach) in order to give confidence that enough participants are available to find a clinically meaningful difference between active dose and placebo if the below assumptions are met.

The primary efficacy endpoint is the percent change from baseline in the PASI score at Week 16. Percent change from baseline relative to placebo will be estimated within the model as (percent change in active) - (percent change in placebo), with a negative value indicating a greater improvement for active than placebo. A percent change from baseline relative to placebo of at least 20% will be considered clinically meaningful. The pooled standard deviation across all doses is assumed to be 25%.

Participants in the placebo arm of each cohort will be pooled for the statistical analysis in order to compare active and control arms resulting in 75 participants randomized to the pooled placebo group and 50 participants randomized to each active treatment group (EDP1815 0.8×10^{11} cells, EDP1815 3.2×10^{11} cells, and EDP1815 8.0×10^{11} cells). Assuming that no more than 15% of participants will discontinue treatment before the Week 16 visit, at least 42 active and 21 placebo participants in each of the 3 cohorts are expected to provide data through the Week 16 visit.

Each pairwise comparison between pooled placebo and active dose would be expected to have more than 95% power to detect a difference between the treatment groups at the 5% significance level under the assumption that pooling the placebo groups is a valid strategy. If the 3 placebo cohorts are considered to be too heterogeneous for pooling into a single reference group, the power to detect a difference in each within-cohort pairwise comparison between active and placebo doses would be greater than 80%.

As the statistical inference for this study will focus on estimation rather than testing a formal hypothesis, no multiplicity adjustments

of the different comparisons between groups in order to control the study-wise type I error rate will be performed.

Similarly, as there is no intention to use any interim analyses to stop the study early for efficacy, no adjustments for multiplicity will be made to account for any analyses performed as part of the interim analyses.

Statistical Methods: Analysis methods for key endpoints are briefly described below. Further details on all analyses will be described in the SAP.

No formal hypothesis will be tested. A model-based probability inference approach in a Bayesian framework will be used to guide decision-making around dose selection. Posterior estimates and 95% credible intervals (CrI) for the difference between each active dose and placebo will be produced for relevant primary and secondary endpoints.

Unless otherwise specified, missing data will be considered as missing at random and will be accounted for using mixed models for repeated measures, with all time points collected for the relevant endpoint included in the model. This includes data which is excluded due to collection after treatment discontinuation or after a protocol deviation as applicable to the definition of the estimands used in the analysis.

The primary analysis for the study will occur after all participants have completed 4 weeks of follow-up after their last dose of study medication (end of Part A). The final analysis for the study will occur when all participants have completed the required relapse and rebound follow-up period of up to 24 weeks post-treatment (end of Part B).

Analysis Sets:

The mITT set will consist of all participants who were randomized to treatment and who received at least one dose of study treatment.

The PPS will consist of all mITT participants who were not replaced (following study withdrawal before the end of Week 4) and who do not have a protocol deviation that may impact efficacy with a start date for the deviation before initiation of study treatment.

The safety set will consist of all participants who received any study drug.

The mITT set will be the primary population of interest for the efficacy section, with some supportive analyses performed using the PPS. The safety set will be used for all safety summaries.

Statistical Analysis Methodology:

Statistical analysis will be performed using SAS software Version 9.3 or later. Continuous variables will be summarized using the mean, standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Time-to-event variables will be summarized using Kaplan-Meier estimates of the proportion of participants with the event at each visit. Data will be listed in data listings.

Analysis of Primary Efficacy Endpoint:

The primary analysis will be performed using a Bayesian MMRM. The model will include parameters for treatment*visit and baseline PASI score*visit interactions. Body mass index, gender, country, and time since diagnosis will also be considered and included as parameters if found to be significant ($p<0.05$). The model will not include an intercept. The priors for all parameters in the model will be non-informative and follow a normal distribution with mean 0 and SD 1000. The prior for the variance-covariance matrix will follow an inverted Wishart distribution with degrees of freedom equal to the number of visits and an identity scale matrix.

The adjusted posterior mean percentage change from baseline and the associated 95% HDP CrI for each treatment at Week 16 will be reported, together with the adjusted mean difference from placebo and the associated 95% HDP CrI for each active dose at each visit and the probability that each treatment difference is less than 0%, -20%, -30%, and -50%.

Analysis of Secondary Efficacy Endpoints:

All secondary analyses will be performed on the mITT set, excluding data collected after treatment discontinuation, without consideration of any protocol deviations. Dose will be treated as a categorical variable and no dose response modelling will be done. Comparisons of interest will be between individual EDP1815 doses and placebo. All p-values, posterior probabilities, CI, and CrI calculated will be considered as descriptive with no further adjustments for multiplicity performed.

Analyses of Exploratory Efficacy Endpoints

Exploratory endpoints will be summarized using the mITT population, with data collected after discontinuation of treatment excluded but without consideration of any protocol deviations.

Analyses of biomarkers will be addressed in a data analysis plan outside the study SAP.

	Pharmacokinetic Analyses: The number and percentage of participants who have a quantifiable concentration of EDP1815 in their blood sample will be summarized using the safety set by visit. Placebo participants will be pooled into a single treatment group. If at least 20% of participants within a treatment group are found to have a quantifiable level at one of the visits, then the concentration will be summarized as a continuous variable for the relevant treatment group at that visit. **Safety Analyses:** All safety endpoints will be tabulated or plotted by treatment group using the safety set. All safety analyses will use the pooled placebo. Further details will be described in the SAP.
Version and Date of Protocol:	Version 5.0 (Amendment 4); 17 November 2020

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BSA	body surface area
BSFS	Bristol Stool Form Scale
CFR	Code of Federal Regulations
CI	confidence interval
COVID	Corona virus disease
CrI	credible interval(s)
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DIC	deviance information criterion
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDP1815	investigational study drug
EMA	European Medicines Agency
EMICM	expectation-maximization iterative complex minorant
EOS	end of study
EU	Europe
FDA	US Food and Drug Administration
FSH	follicle-stimulating hormone
FUP	functional uniform prior
GCP	Good Clinical Practice
GI	gastrointestinal
HbsAg	hepatitis B surface antigen
HCG	human chorionic gonadotropin
HCV	hepatitis C virus

Abbreviation	Definition
HDL	high-density lipoprotein
HDP	high-density probability
HIV	human immunodeficiency virus
HPMC	hydroxypropyl methylcellulose
HRT	hormone replacement therapy
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IFNγ	interferon gamma
IL	interleukin
IM	intramuscular
IMP	investigational medicinal product
IRB	institutional review board
IRE	Ireland
IRT	interactive response technology
LDL	low-density lipoprotein
LSS	lesion severity score
MCV	mean corpuscular volume
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed effects model with repeated measures
mNAPSI	modified Nail Psoriasis Severity Index
mRNA	messenger RNA
MTX	methotrexate
OTC	over-the-counter
PASI	Psoriasis Area and Severity Index
PCR	polymerase chain reaction
PDE4	phosphodiesterase type 4
PGA	Physician's Global Assessment

Abbreviation	Definition
PIC	powder in capsule
PPS	per-protocol set
PSI	Psoriasis Symptom Inventory
QTcF	QT interval corrected using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SF-36 BPS	SF-36 Bodily Pain Scale
SoA	schedule of assessments
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TNFα	tumor necrosis factor alpha
UK	United Kingdom
ULN	upper limit of normal
USA	United States of America
VAS	visual analog scale
WHO	World Health Organization
WOCBP	woman/women of child-bearing potential

1 Introduction

Evelo Biosciences Inc. (Evelo) is developing medicines based on single strains of bacteria as a new class of therapeutic agents. These therapeutic agents are human commensal organisms that offer the potential of systemic immune system modulation following oral administration, without systemic exposure. EDP1815 is a pharmaceutical preparation of a strain of *Prevotella histicola* isolated from a human duodenal biopsy: it has not been genetically modified. Strains of the *Prevotella* genus of microbes have been found in all human populations tested to date, at abundances ranging from less than 1% to nearly 50% of total fecal microbial load (Vandeputte 2017). *Prevotella* are gram-negative, obligate anaerobes that are natural human commensals in the oral cavity and GI tract. EDP1815 is a gram-negative bacterium sensitive to the major classes of antibiotics, eg, penicillins and cephalosporins. In non-clinical and clinical studies, its therapeutic effects have been dose-dependent. The IB describes the development of EDP1815, initially in the treatment of psoriasis and atopic dermatitis. Initial clinical data from the first-in-human study in psoriasis patients are presented in the IB (Evelo Biosciences 2019).

Several studies (de Groot et al 2017; Hindson et al 2017; Yan et al 2017; Felix et al 2018) suggest that host-microbe interactions in the gut, and particularly in the small intestine, can influence systemic inflammation. Evelo is seeking to develop oral anti-inflammatory medicines based on this emerging science. Preclinical data confirms that individual strains of microbes exhibit unique pharmacological profiles. This is thought to be based on multiple distinct microbial structural pattern motifs interacting with varying combinations of host pattern recognition receptors in small intestinal epithelium.

Studies of EDP1815 in vitro in a range of human and mouse assays and studies in vivo in model symptoms support the use of EDP1815 in the treatment of inflammatory diseases including psoriasis (Evelo Biosciences 2019). EDP1815 increases secretion of anti-inflammatory cytokines such as IL-10, IL-1RA, and IL-27 from human immune cells, while inducing minimal production of pro-inflammatory cytokines such as IL-6, TNFα, and IFNγ.

Oral administration of EDP1815 to mice results in striking pharmacodynamic effects on animal models of delayed-type hypersensitivity, fluorescein isothiocyanate cutaneous hypersensitivity, collagen-induced arthritis (Marietta et al 2016) and experimental acute encephalomyelitis (Mangalam et al 2017). The high degree of consistency of both effect and

dose suggests the potential for clinical benefit across multiple type 1, type 2, and type 3 inflammatory conditions. No potentially related adverse effects were seen in the animals used in these experiments with daily dosing for up to 3 weeks or with alternate day dosing for over 7 weeks. Immunophenotyping ex vivo in these models shows increased regulatory T cell numbers and regulatory dendritic cells in spleen and mesenteric lymph nodes, as well as decreases in pro-inflammatory cytokines such as IL-23p40, IL-17, TNFα, IL-6, and IL-13. Treatment also led to enhancement of gut intestinal barrier integrity, which is often disrupted in patients with inflammatory diseases. These effects on immune parameters have been observed both within and outside the GI tract, which demonstrates that host-microbe interactions in the gut can affect the immune response in peripheral tissues.

Psoriasis is a chronic immune-mediated type 1/3 inflammatory skin disease in which hyperactive T cells trigger excessive keratinocyte proliferation. This results in the formation of raised erythematous plaques with scaling. Psoriatic lesions can appear anywhere on the body but are most often seen on the knees, elbows, scalp, and lumbar area. Critical events in the inflammatory process include activation of Langerhans cells and T cells, selective trafficking of activated T cells to the skin, and induction of an inflammatory cytokine and chemokine cascade in skin lesions. Clinical data have validated the role of anti-TNFα, anti-IL-17, and anti-IL-23 therapy in moderate to severe psoriasis. For patients with mild to moderate psoriasis, therapy usually involves topical agents (topical corticosteroids, vitamin D3 analogs), with topical corticosteroids providing the greatest range of efficacy and a wide range of formulations. More recently, physicians are prescribing apremilast, a first-in-class oral PDE4 inhibitor, ahead of biological therapy, which includes etanercept, infliximab, adalimumab, ustekinumab, and secukinumab.

In Evelo study EDP1815-101, a total of 56 participants have participated in Cohorts 1-4, with 36 of these participants receiving EDP1815 once daily; 16 of these were treated for 14 days (healthy volunteers) and 20 participants with psoriasis were treated for 28 days. Clinical responses, similar to apremilast and tofacitinib at the same time point, have been observed on the (psoriatic) LSS and PASI at Day 28. Furthermore, at the Day 42 follow-up visit, when participants were “off treatment” for 14 days, there was continued improvement in the pharmacodynamic response as measured by both LSS and PASI for participants administered the higher dose, but not the lower dose, suggesting a dose relationship on the durability of effect. The safety profile of EDP1815 was similar to placebo, with no SAEs or AEs of severe intensity.

The evidence available so far suggests EDP1815 is very well tolerated and it continues to undergo clinical development in mild to moderate psoriasis. A well-tolerated oral therapy could offer significant benefit in the treatment of psoriasis and it is presently anticipated that EDP1815 would be used in established but early disease, before the use of biologic therapies.

This Phase 2 study has been designed to investigate the clinical safety and efficacy of EDP1815 and to identify an optimal dose.

2 Study Objectives

All objectives are related to understanding the safety, efficacy, and dose effects of EDP1815 treatment of mild to moderate plaque psoriasis in adult participants (Section 4.1).

2.1 Primary Objective

The primary objective of this study is to evaluate the safety and efficacy of 3 different doses of EDP1815 for the treatment of psoriasis following daily dosing for 16 weeks.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To evaluate the efficacy dose response of EDP1815 at Week 16
- To evaluate the maximal clinical benefit of EDP1815 at Week 16
- To evaluate the optimal dose of EDP1815 based on efficacy and safety up to Week 16
- To evaluate the safety and tolerability of EDP1815 (all dose levels) throughout the study
- To evaluate relapse and rebound of plaque psoriasis after cessation of EDP1815

2.3 Exploratory Objectives

The exploratory objectives of this study are the following:

- To evaluate the time to onset of clinical response to EDP1815
- To evaluate the effect of EDP1815 treatment on patient-reported outcomes including quality of life and pain
- To evaluate the duration of remission, treatment success, and therapeutic effect of EDP1815

- To evaluate the effect of EDP1815 treatment on biomarkers in blood
- To evaluate the effect of EDP1815 treatment on biomarkers in skin plaques
- To evaluate the effect of EDP1815 treatment on fecal microbiome composition

3 Investigational Plan

3.1 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-cohort, dose-ranging study of participants with mild to moderate plaque psoriasis (Section 4.1).

Part A of the study comprises a screening period of up to 4 weeks, a baseline visit, a treatment period of 16 weeks (8 planned study site visits), and a follow-up visit at Week 20 (4 weeks after cessation of dosing). Part A of the study therefore comprises a total of 11 scheduled study visits, and on completion of Part A, the primary analysis will be performed.

Part B of the study is designed to assess the durability of treatment response and incidence of rebound of psoriasis following cessation of dosing. All participants will attend for skin assessments at Weeks 24 and 28, unless they have previously experienced treatment failure and/or had rebound of disease. A final visit at Week 40 will also be performed for those participants who experienced treatment response at Week 16 of treatment, but have not yet met the definition of disease relapse. Part B of the study therefore comprises a maximum of 3 additional scheduled study visits with a follow-up of up to 40 weeks (24 weeks after cessation of dosing), and on completion of Part B, the final analysis will be performed.

The study design is presented in Figure 3-1, and the SoA is presented in Table 6-1 for Part A, and in Table 6-2 for Part B.

After eligibility is confirmed during the screening period (Section 4.1), participants will be randomly assigned in a 1:1:1 ratio to 1 of the following 3 parallel cohorts:

- Cohort 1: 0.8×10^{11} cells of EDP1815 or matching placebo administered as 1 PIC, once daily (Section 5.2).
- Cohort 2: 3.2×10^{11} cells of EDP1815 or matching placebo administered as 4 PICs, once daily (Section 5.2).
- Cohort 3: 8.0×10^{11} cells of EDP1815 or matching placebo administered as 10 PICs, once daily (Section 5.2).

In each cohort, approximately 75 participants will be randomly assigned in a 2:1 ratio to receive either EDP1815 or matching placebo once daily for 16 weeks.

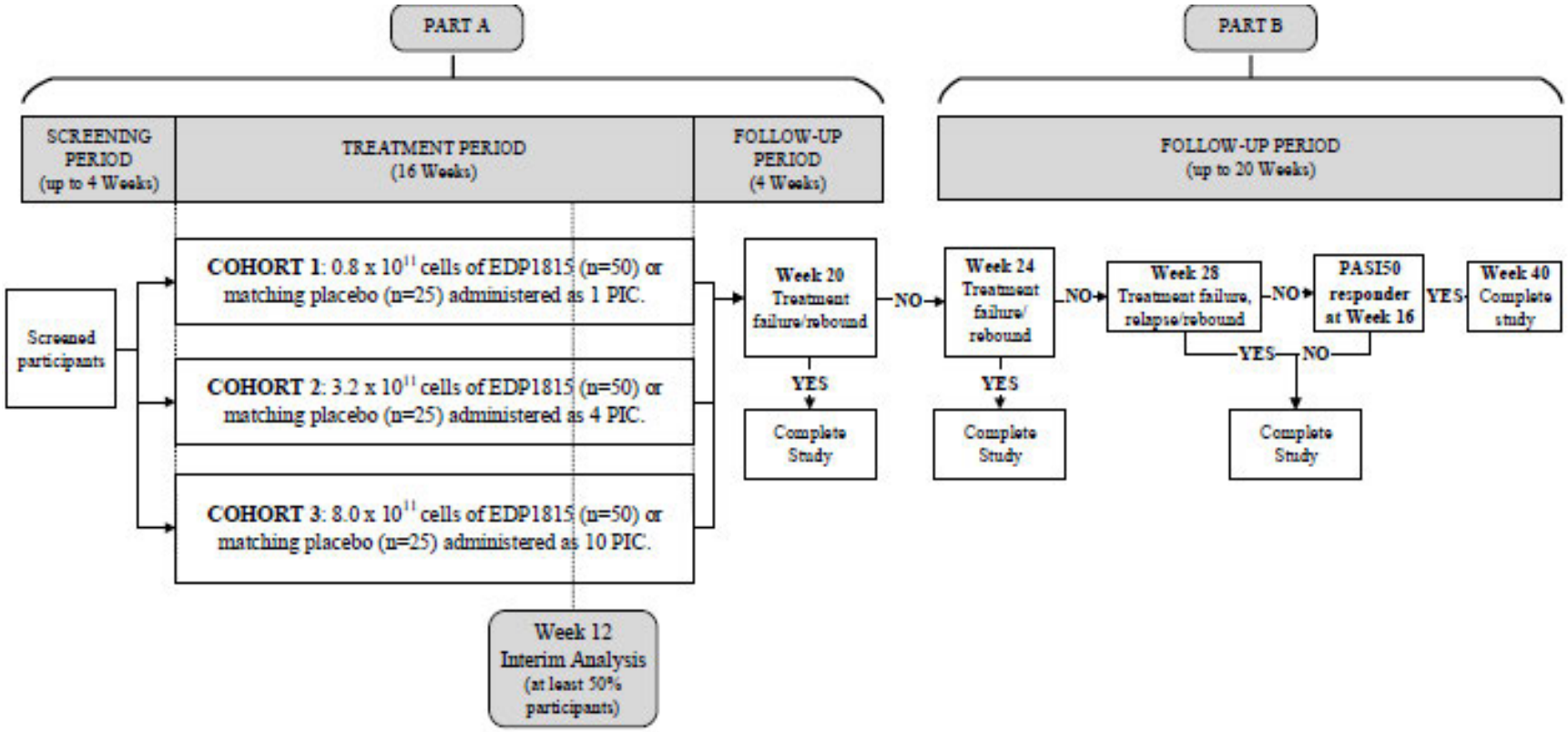
An interim analysis may be performed after at least 50% of participants have completed at least 12 weeks of treatment (Section 7.6.7).

After the planned 16 weeks of treatment, all participants will have an initial follow-up visit at Week 20 (ie, 4 weeks post last dose of study treatment), completing Part A of the study; and enter Part B with continued follow-up for a maximum of 20 additional weeks (up to Week 40). The duration of follow up will depend on the initial response to study therapy and any relapse or rebound experienced after cessation of study treatment.

The maximum planned duration of study participation will be 44 weeks, and the duration of the study is defined for each participant as the date signed written informed consent is provided through to their last follow-up visit. Participants will be considered to have completed the study after the completion of all required visits.

The EOS is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA.

Figure 3-1 Study Design



Note: All dosing is once daily.

3.1.1 Rationale for Study Design

The EDP1815 Phase 1 program evaluated doses of 1.6×10^{10} cells to 8.0×10^{11} cells given daily for 2 weeks in healthy volunteers and doses of 1.6×10^{11} cells and 8.0×10^{11} cells given daily for 4 weeks to participants with mild to moderate psoriasis. All doses were found to be well tolerated and doses of both 1.6×10^{11} and 8.0×10^{11} cells induced clinically relevant reductions in signs and symptoms of plaque psoriasis and psoriasis lesion severity.

The doses tested in the program are based on predictions from the preclinical data and the clinical and biomarker data obtained in EDP1815-101, the Phase 1 study. All doses tested up to 8.0×10^{11} cells have been equally well tolerated. No clear difference in efficacy was observed between the 1.6×10^{11} cells and the 8.0×10^{11} cells in EDP1815-101 over the 28-day dosing period, but at the 14-day follow up (Day 42) the participants receiving the higher dose had a continued improvement in their psoriasis compared to participants who had received the lower dose. This suggests a more sustained and potentially deeper response in the high dose group. Evelo is therefore proposing to include the lowest and highest feasible doses (based on capsule load) in this study to establish the dose response, the maximum clinical benefit, and to assess participant tolerability and acceptability of the doses tested.

The clinical response to EDP1815 treatment will be evaluated using multiple assessments, facilitating appropriate selection of efficacy measures for future studies.

The use of a placebo comparator is appropriate for this participant population of individuals with mild to moderate plaque psoriasis for the following reasons:

- The limited proven efficacy of other treatments (topical corticosteroids, vitamin D3 analogs, and apremilast) in patients with mild to moderate plaque psoriasis that could potentially serve as an active comparator
- The limited duration of the study (maximum of 16 weeks of treatment) for each participant
- A randomization ratio of 2:1 for EDP1815 treatment to placebo treatment in each cohort

Part B of the study, which includes additional visits at Weeks 24, 28, and 40, is designed to help understand the durability of treatment effect, including time to relapse and incidence of

any rebound of psoriasis after treatment has completed. These are important aspects to understand regarding a psoriasis therapy (EMA guideline CHMP/EWP/2454/02, 2004).

4 Participant Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 225 participants will be randomized in multiple countries, including (but not limited to) sites in the United States, the United Kingdom, Poland, and Hungary. Participants will be assigned to study treatment only if they meet all inclusion criteria and no exclusion criteria during screening.

Deviations from the inclusion and exclusion criteria are not allowed: adherence to the eligibility criteria as specified in the protocol is essential.

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study drug (EDP1815 or placebo). A minimal set of screen failure information is required to be entered in the eCRF to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who fail to satisfy inclusion and exclusion criteria at screening may be rescreened 1 additional time with the agreement of the medical monitor before rescreening. Participants may also be rescreened if they initially pass the screening assessments but go beyond the screening period time limit. In exceptional circumstances, the screening window can be extended on a case-by-case basis after consultation with the sponsor: such an exceptional extension will not be considered a protocol deviation.

4.1.1 Inclusion Criteria

Each participant must meet all the following criteria to be enrolled in this study:

1. Give written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements.
2. Males or females ≥18 and ≤70 years old at the time of informed consent.
3. A documented diagnosis of plaque psoriasis for ≥6 months.

4. Have mild to moderate plaque psoriasis with plaque covering BSA of ≥3% and ≤10% and meet **both** of the following additional criteria:

    a. PASI score of ≥6 and ≤15, and

    b. PGA score of 2 or 3.

    All parameters in this criterion should be reconfirmed at baseline visit prior to randomization.

5. Meet the following contraception criteria:

    a. Male participants:

        i. A male participant must agree to use contraception as detailed in Appendix 13.1 of this protocol during their participation in this study and for a period of 90 days after the last dose and refrain from donating sperm during this period.

    b. Female participants:

        i. A female participant is eligible to participate if she is not pregnant (Appendix 13.1), not breastfeeding, and at least 1 of the following conditions applies:

            1. Not a WOCBP as defined in Appendix 13.1, OR

            2. A WOCBP who agrees to follow the contraceptive guidance in Appendix 13.1 during their participation in this study, 28 days prior to the first dose and for at least 1 complete menstrual cycle (≥28 days) after the last dose.

6. Agrees to not increase their usual sun exposure during the study.

4.1.2 Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

1. Have received EDP1815 within the 3 months prior to screening.
2. Have a diagnosis of non-plaque psoriasis.
3. Plaque psoriasis restricted to scalp, palms, and soles only.

4. Evidence of skin conditions that would interfere with psoriasis evaluation or treatment response (eg, atopic dermatitis, fungal or bacterial superinfection).
5. Have received systemic immunosuppressive therapy (MTX, apremilast, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, and tacrolimus) within 4 weeks of first administration of study drug.
6. Unresponsive to prior use of biologics (including, but not limited to, TNFα inhibitors, natalizumab, efalizumab, anakinra or agents that modulate B cells or T cells).
7. If prior biologic therapy and responsive, participants must have been off therapy for at least 12 months prior to first administration of study drug.
8. Have received phototherapy or any systemic medications/treatments that could affect psoriasis or PGA evaluation (including, but not limited to oral or injectable corticosteroids, retinoids, psoralens, sulfasalazine, hydroxyurea, or fumaric acid derivatives) within 4 weeks of first administration of study drug. This includes therapeutic doses of non-steroidal anti-inflammatory drugs such as ibuprofen, although intermittent as required use as an analgesic is permitted when required. Chronic use of low dose aspirin for cardiovascular protection is permitted.
9. Currently receiving lithium, antimalarials, leflunomide, or IM gold, or have received lithium, antimalarials, IM gold, or leflunomide within 4 weeks of first administration of study drug.
10. Have used topical medications/treatments that could affect psoriasis or PGA evaluation (including [but not limited to] high- and mid-potency corticosteroids [Appendix 13.2], anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, picrolimus, and tacrolimus) within 2 weeks of the first administration of study drug. Topical unmedicated emollients and low-potency topical corticosteroids are not excluded.
11. Gastrointestinal tract disease (eg, short-bowel syndrome, diarrhea-predominant irritable bowel syndrome) that could interfere with GI delivery and transit time.
12. Active inflammatory bowel disease.
13. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Day 1 (Visit 2).

14. Have received live or live-attenuated replicating vaccine within 6 weeks prior to screening or intend to have such a vaccination during the study.
15. Clinically significant abnormalities in screening laboratory values that would render a participant unsuitable for inclusion (per investigator judgment).
16. For women, serum creatinine ≥125 µmol/L (1.414 mg/dL); for men, serum creatinine ≥135 µmol/L (1.527 mg/dL).
17. ALT and AST >2 × ULN.
18. Known history of or positive test for HIV, or active infection with hepatitis C or chronic hepatitis B.
19. History of clinically significant acute cardiac or cerebrovascular event within 6 months before screening (includes stroke, transient ischemic attack, and coronary heart disease [angina pectoris, myocardial infarction, heart failure, revascularization procedures]).
20. In the opinion of the investigator, evidence of clinically important cardiac conduction abnormalities at screening as judged by ECG.
21. Current acute or chronic inflammatory disease other than psoriasis or psoriatic arthritis (eg, inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus). If a subject is off all treatment and is disease and has been symptom free for greater than 12 months, then the inflammatory disease is considered to be in remission and they may be enrolled.
22. Hypersensitivity to *P histicola* or to any of the excipients.
23. Active untreated mental or psychiatric disorder. Participants who are on stable dosing of medication for a mental or psychiatric disorder for at least 6 months before screening and whose treating physicians consider them to be mentally stable may be enrolled.
24. Any major or minor GI surgery within 6 months of screening.
25. Any major surgery within 6 months of screening.
26. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.

27. Treatment with another investigational drug, biological agent, or device within 1 month of screening, or 5 half-lives of investigational agent, whichever is longer.
28. Initiating any OTC or prescription medication including vitamins, herbal supplements and nutraceuticals (eg, supplements including high doses of probiotics and prebiotics as usually found in capsules/tablets/powders), except acetaminophen/paracetamol and anti-histamines, within 14 days prior to baseline or anticipates change in dosage for the duration of the study period.
    Note: Probiotic and prebiotic foods that contain low doses are allowed (eg, yoghurt, kefir, kombucha), however, supplements containing high doses of probiotics and prebiotics are not allowed at any point during the study.
29. Blood donation of >100 mL within 30 days of screening or >499 mL within 12 weeks of screening.
30. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol or unwillingness to cooperate fully with the investigator.
31. Have any other conditions, which, in the opinion of the investigator or sponsor, would make the participant unsuitable for inclusion or could interfere with the participant participating in or completing the study.

4.2 Discontinuation From Study Treatment and/or Withdrawal From the Study

Participants may discontinue from study treatment or withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep participants in the study. The reasons for participants discontinuing treatment and/or withdrawing from the study will be recorded in the eCRF.

There are 3 scenarios that result in interruption of the treatment regimen: interruption of study drug, early discontinuation of study drug, and early withdrawal from the study:

- Interruption of treatment is defined as a temporary stopping of study drug that resumes during the treatment period, due to an AE or any other reason. The maximum permitted interruption is 1 week.

- Early discontinuation of treatment is defined as permanent stopping of study drug before completing the visit scheduled for Week 16. Investigators will strive to ensure that a participant who has interrupted treatment for a particular reason will not discontinue treatment unless discontinuation is medically imperative in the investigator's judgment. However, a dose interruption of more than 1 week will result in mandatory discontinuation of treatment.

- Early withdrawal from the study is defined as failing to complete the required follow-up period.

A participant will be discontinued from the study drug or withdrawn from the study for any of the following reasons:

1. The participant experiences treatment failure, demonstrated by the participant commencing an oral agent, biological, or intermediate or high-potency topical therapy.
2. The participant has a serious or intolerable AE that in the investigator's opinion requires discontinuation from study treatment or withdrawal from the study.
3. The participant has symptoms or an intercurrent illness not consistent with the protocol requirements or that justifies withdrawal.
4. The participant is lost to follow-up.
5. Other reasons (eg, pregnancy, development of contraindications to use of study drug).
6. The participant withdraws consent, or the investigator or sponsor decides to discontinue the participant's participation in the study.

A participant may be discontinued from the study drug or withdrawn from the study for any of the following reasons:

1. The participant is noncompliant with the protocol.
2. The participant has laboratory safety results that reveal clinically significant hematological or biochemical changes from the baseline values.
3. If the participant is required to start therapy for a concurrent condition that may affect the study endpoints, eg, a disease-modifying agent for psoriatic arthritis.

In all of these instances, if the participant is to remain in the study, then the investigator should confirm that the participant is suitable to continue in the study with the medical monitor.

4.2.1 Discontinuation From Study Treatment

It may be necessary for a participant to permanently discontinue study treatment. If study drug is definitively discontinued, the participant will be encouraged by the investigator to continue to participate in all scheduled study site visits and assessments, so that study data will be collected for the participant per protocol. Every effort should be made to keep participants in the study.

Dosing may be interrupted at the investigator's discretion due to AE or intercurrent illness for a period of up to 1 week, following which the participant may resume treatment if the investigator considers it safe to do so. The participant should discontinue treatment permanently if the AE occurs a second time.

4.2.2 Withdrawal From the Study

Participants may withdraw from the study at any time at their own request or they may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. The investigator will also withdraw a participant if Evelo terminates the study.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the eCRF.

Participants who withdraw from the study during Part A should complete the final assessments listed under the Follow-up Visit (Week 20) at an unscheduled follow-up visit, as detailed in the SoA (Table 6-1). Participants who withdraw from the study during Part B should complete the final assessments at the Early Withdrawal Visit, as detailed in Table 6-2.

4.2.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 2 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the eCRF.

If the participant continues to be unreachable, he/she will be considered to have withdrawn from the study.

4.2.4 Replacements

Participants who withdraw or are withdrawn from the study within 4 weeks of randomization may be replaced in order to have approximately 225 participants provide at least 4 weeks of postbaseline data.

Replacement participants will be randomly assigned treatment in the respective cohorts of the participants they replace.

5 Study Treatments

5.1 Method of Assigning Participants to Treatment Groups

Participants will be randomly assigned at the baseline visit (Visit 2) to 1 of 3 cohorts (in a 1:1:1 allocation ratio) that are distinguishable to participants and study staff by the number of capsules administered per once-daily dose. Within the cohort, participants will be randomly assigned in a 2:1 allocation ratio to receive either EDP1815 or matching placebo treatment (Section 3.1). Interactive response technology will be used to administer the randomization schedule.

5.2 Treatments Administered

Participants in each cohort (described in Section 3.1) will self-administer study drug doses orally in the morning with water, refraining from consuming acidic drinks 1 hour either side of dosing and from eating 2 hours before dosing and 1 hour after dosing (Table 6-1). The composition of capsules is described in Section 5.3. Strategy to improve compliance is presented in Section 5.7.

5.3 Identity of Study Drug

The EDP1815 drug product is available as enteric-coated HPMC hard capsules in Swedish-Orange color. The EDP1815 PIC consists of freeze-dried powder of *P histicola*, mannitol, magnesium stearate, and colloidal silicon dioxide. Each EDP1815 PIC contains 8.0×10^{10} cells of *P histicola*.

The matching placebo is identical in appearance but do not contain *P histicola* or any other bacteria. The placebo excipients include microcrystalline cellulose and magnesium stearate.

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

EDP1815 PICs and matching placebo will be prepared in blister wallets of 10 capsules. Blister wallets will be packaged in packs that contain approximately 1 week's supply of study drug for 1 randomized participant, identified by a numeric code. When appropriate for the interval between study visits, multiple packs will be assigned and dispensed for each participant throughout the treatment period.

Study drug (EDP1815 and placebo) must be stored in a secure area (eg, a locked refrigerator) and kept at a controlled temperature of 2°C to 8°C. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit and during storage at each site for all study drug received and any discrepancies are reported and resolved before use of the study drug.

[redacted] will supply study drug to each site in non-study descript shipping containers that will maintain temperature during transit within 2°C to 8°C. Temperature monitoring devices will be used to confirm adequate transit temperature. Site procedure for receipt of study drug will be provided in the IMP handling manual.

5.4.2 Study Drug Accountability

The investigator will maintain accurate records of receipt of all study drug, including dates of receipt. In addition, accurate records will be kept regarding when and how much test article is dispensed and used by each participant in the study. Study drug will be assigned using an IRT system. Only participants enrolled in the study may receive the study drug and only authorized site personnel may supply the study drug. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable regulations. Further guidance and information for the final disposition of unused study drug are provided in the IMP handling manual. Accountability, reconciliation, and then shipment for destruction or for destruction on site will be documented through the IRT.

5.4.3 Other Supplies

Evelo will supply Bristol stool diaries (Section 6.2.2) and paper dosing diaries to all participants (Section 5.7.1). Electronic devices for administering questionnaires will be provided to all study sites.

5.5 Overdose Management

An overdose is any dose of study treatment given to a participant or taken by a participant that exceeds the maximum dose described in the protocol (10 capsules per day).

Participants will be instructed to contact the investigator or study coordinator immediately in the event of a suspected overdose. In the event of overdose, the appropriate supportive clinical care must be provided as dictated by the participant's clinical status.

Any overdose must be promptly reported to [redacted]. Overdose itself is not to be reported as an AE. However, any AEs or SAEs associated with the overdose are to be reported on relevant AE/SAE sections in the eCRF and on the Paper SAE Form provided to [redacted] (Section 6.2.1).

In the event of a symptomatic overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Document the quantity of the excess dose in the eCRF.
3. Document the overdose symptoms and their duration in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

5.6 Blinding

Study drug will be double-blinded. All study drug (EDP1815 and placebo) will be supplied in identical packaging, color, smell, and appearance to enable double-blinded conditions that ensure all investigators, study site staff, participants, and clinical monitors will remain blinded throughout the study. The IRT system will assign study drug to participants at the time of randomization. Only personnel supporting the IRT system, the independent randomization team, and clinical supplies will be unblinded and will have access to treatment assignments; all other parties involved in the study will be fully blinded.

For the interim analysis, unblinded aggregate results will be produced by an unblinded team within [redacted] and reviewed by Evelo personnel for strategic planning use. These will not be shared with any study site staff, participants, or clinical monitors who will be involved in the collection and review of individual study data.

The data will be unblinded and the primary analysis will be performed once all participants have completed 4 weeks of post-treatment follow-up at Visit 11 (Week 20; at the end of

Part A). Study site staff, participants, and clinical monitors who will be involved in the collection and review of individual study data will remain blinded until Part B is completed.

5.6.1 Breaking the Blind

A participant's treatment assignment will not be unblinded for the investigator or study site staff until EOS unless medical treatment of the participant depends on knowing the study treatment the participant received. In the rare event that unblinding is needed because of a medical emergency, the investigator may unblind an individual participant's treatment allocation through the IRT. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's study treatment assignment unless this could delay emergency treatment of the participant. If a participant's study treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. Reasons for treatment unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

Participants who are unblinded will be allowed to continue their participation in the study; however, any data collected after the unblinding occurred will be excluded from per-protocol analyses.

The Clinical Safety team at [redacted] will be unblinded to study treatment to facilitate appropriate identification and reporting of SUSARs to Competent Authorities and the relevant IECs/IRBs.

5.7 Compliance With Study Treatment

Participant compliance will be determined from capsule counts of unused capsules according to the SoA (Table 6-1).

At each visit during the treatment period (Visit 2 through Visit 9), study site staff will remind the participant of the need to self-administer the capsules as directed and store the study drug according to label instructions.

Before each visit (Visit 3 through Visit 10), study site staff will call participants to remind them to bring all study drug in the original containers to the study site for their visit, and to remind them to also bring their dosing diaries (Section 5.7.1).

Compliance will be assessed by counting returned capsules during the site visits indicated in the SoA (Table 6-1), and the counts will be documented in the source documents and eCRF. Deviation from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of study drug capsules dispensed to and taken by each participant must be maintained and reconciled with the study drug and compliance records. Study treatment start and stop dates, including dates for study treatment delays and/or dose reductions, will also be recorded in the eCRF.

5.7.1 Dosing Diaries

The primary purpose of the diary is to enhance participant compliance with the protocol. Participants will be asked to capture the following information in the diaries:

- Dates of dosing with study drug
- Times of dosing with study drug
- Numbers of capsules in dose
- Changes in concomitant medications
- Changes in symptoms
- Other comments

Diaries will be dispensed and collected as detailed in the SoA (Table 6-1). Study staff will review the diaries with participants at each visit when diaries are collected. Diaries will be reviewed for completeness and accuracy, and participants will be coached as needed on compliance with the protocol.

5.8 Prior, Concomitant, and Rescue Medications

Use of all concomitant medications will be recorded in the participant's eCRF. The minimum requirement is that drug tradename, total daily dose, and the dates of administration are to be recorded. In addition, it is expected that the reason for use and dosage information (including dose and frequency) will also be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and OTC medications. Any changes in concomitant medications also will be recorded in the participant's eCRF. The participant's dosing diary may contain information relevant to the documentation of changes in concomitant medication.

Any concomitant medication or therapy deemed necessary for the welfare of the participant during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF.

5.8.1 Prior Therapy

Prior therapies restricted for participants eligible for this study are detailed in the exclusion criteria (Section 4.1.2).

5.8.2 Concomitant Therapy

Anti-histamines and acetaminophen/paracetamol following labeled dosing instructions are permitted for use at any time during the study. Topical unmedicated emollients and low-potency topical steroids are also permitted if participants were already using them as part of their care prior to study entry (exclusion criterion #10, Section 4.1.2). Participants will be advised to continue to use these therapies as they were prior to study entry.

Non-live and non-replicating vaccines are permitted in this study.

Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required.

5.8.2.1 Prohibited Concomitant Therapy

Prior therapies restricted for participants eligible for this study as detailed in the exclusion criteria (Section 4.1.2) are prohibited concomitant therapy during the study.

Live or live-attenuated replicating vaccines are contra-indicated in this study.

5.8.3 Rescue Medicine

Although *P histicola* is a natural human commensal in the human GI tract, if a rare overgrowth condition is suspected the following rescue antibiotics may be used (supplied by the study site) if the clinical situation warrants such use:

1. Penicillin V
2. Amoxicillin

Or, if allergic to the above antibiotics:

3. Macrolides (eg, clarithromycin or erythromycin)
4. Tetracyclines (eg, doxycycline)

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the eCRF.

5.9 Dose Modification

Dose adjustments, including dose interruptions, and/or decreasing the dose frequency may be allowed for safety or tolerability (including capsule load) after consultation with the sponsor medical monitor.

6 Study Assessments and Procedures

Before performing any study procedures, all potential participants will sign an ICF. Additional procedural details related to the ICF are provided in Section 9.3.

The SoA is presented in Table 6-1. Detailed instructions for study site activities will be provided in the appropriate specific user manual, where applicable. High level descriptions of the study assessments are presented in the subsections of Section 6. In exceptional circumstances, study assessments may be conducted remotely (ie, at a participant's home), except for screening, baseline, Visit 9, and Visit 10. Remote visits can only occur if operationally possible.

Table 6-1 Schedule of Assessments – Part A

Procedure	Screening	Baseline	Treatment Period								Follow-up[a, b]
Day	**-28 to -7**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**85**	**113**	**141**
Week	**-4**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**20**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Visit window (days)	**--**	**--**	**5-11**	**12-18**	**19-25**	**26-32**	**40-46**	**54-60**	**82-88**	**110-116**	**141-148**
Informed consent	X										
Inclusion and exclusion criteria	X	X [c]									
Demography	X										
HbsAg, HCV and HIV screening	X										
HLA sample [d]		X									
Medical history and current medical conditions (including duration of psoriasis)	X	X									
Full physical examination (height only at screening) [e]	X	X	X			X			X	X	X
Pregnancy test [f]	X	X								X	X
Laboratory assessments (hematology, serum biochemistry and CRP, and urinalysis)	X	X				X		X	X	X	X
Fasting [g] blood sampling		X						X		X	
12-lead ECG [h]	X	X				X				X	X
Vital signs [i]	X	X	X	X	X	X	X	X	X	X	X
Randomization		X									
Dosing [j]		X	X	X	X	X	X	X	X	X	
Dispense study drug		X	X	X	X	X	X	X	X		
Collect/count unused study drug			X	X	X	X	X	X	X	X	
Skin plaque biopsies [k]		X								X	

Procedure	**Screening**	**Baseline**	**Treatment Period**								**Follow-up[a, b]**
Day	**-28 to -7**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**85**	**113**	**141**
Week	**-4**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**20**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Visit window (days)	**--**	**--**	**5-11**	**12-18**	**19-25**	**26-32**	**40-46**	**54-60**	**82-88**	**110-116**	**141-148**
Digital photography of lesion sites [l]		X				X		X		X	X
Stool samples for microbiome investigation [m]		X								X	X
Dispense stool diary	X										
Collect/record stool diary		X									
Blood sample for detection of systemic EDP1815		X								X	
Samples for blood biomarkers		X								X	
BSA involvement (%), PGA, PASI [n, o]	X	X	X	X		X		X	X	X	X
LSS, mNAPSI [n]		X	X	X		X		X	X	X	X
PSI, DLQI, PA-VAS, SF-36 (vitality and pain), Fatigue [p]		X	X	X		X		X	X	X	X
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X
Dispense dosing diary		X	X	X	X	X	X	X	X		
Collect/review dosing diary [q]			X	X	X	X	X	X	X	X	

[a] Participants who withdraw from the study during Part A should complete the final assessments listed under the Follow-up Visit (Week 20), at an unscheduled follow-up visit. Where relevant and when possible, this should be arranged within 72 hours of the start of a new psoriasis treatment. In the event of early withdrawal from the study, unused study drug is to be collected/counted at this visit.

[b] All participants will attend additional follow-up Visits 12 and 13 (see Table 6-2), unless they are considered a 'treatment failure' or meet the criteria for rebound.

[c] Recheck inclusion/exclusion criteria at Baseline, before first dose of study drug. Screening laboratory results will be used to confirm eligibility at Baseline/Visit 2 (ie, Day 1).

[d] Predose optional genetic samples.

[e] BMI will be calculated from the height and weight.

[f] Women of child-bearing potential only. Serum HCG at screening, urine thereafter. Pregnancy testing will be performed at the visits indicated or if a menstrual cycle is missed or if pregnancy is otherwise suspected.

[g] Participants will fast for at least 8 hours before glucose and lipid blood sampling

[h] A single ECG tracing is to be obtained on the day of the visit. If, in the opinion of the investigator, there appear to be clinically significant findings, a second tracing should be obtained during the visit.

[i] Blood pressure, pulse, respiratory rate, and temperature are to be checked on the day of the visit.

[j] The first dose will be given at the baseline visit, following random assignment to treatment. Subsequent doses are to be taken (away from the study site) once daily in the morning at approximately the same time ±2 hours. Participants should refrain from consuming acidic drinks 1 hour either side of dosing and from eating 2 hours before dosing and 1 hour after dosing. On days of study site visits during the treatment period (Visit 3 through Visit 10, inclusive), participants may dose at home.

[k] Skin plaque biopsies (ie, a 4 mm punch biopsy, performed pre-dose by suitably trained study personnel and processed as per laboratory manual) are to be performed after all other assessments have been completed at the end of Visits 2 and 10.

[l] Digital photographs should be taken of up to 6 lesion sites that have a lesion area ideally greater than 2 cm by 2 cm at baseline. The same locations photographed at baseline should be followed throughout the study for each participant.

[m] Stool samples are to be collected within the 48 hours preceding each visit of stool sample collection.

[n] Investigator rating scales. Participants will be asked to withhold all emollients or moisturizers on the day of these study visits until all study assessments are completed.

[o] Inclusion criterion #4 (mild to moderate plaque psoriasis with plaque covering BSA of ≥3% and ≤10%, PASI score of ≥6 and ≤15, and PGA score of 2 or 3) should be reconfirmed at the baseline visit prior to randomization.

[p] Participant-reported assessments.

[q] Study staff will review the dosing diaries with participants at each visit when diaries are collected. Diaries will be reviewed for completeness and accuracy, and participants will be coached as needed on compliance with the protocol.

Table 6-2 Schedule of Post-Treatment Follow-Up Assessments – Part B

Procedure	**Post-Treatment Follow-Up – Part B** [a]			
Visit number	**12** [b]	**13** [b]	**14** [c]	**Early Withdrawal Visit**[a]
Months (after the End of Treatment)	**2**	**3**	**6**	
Weeks	**24**	**28**	**40**	
Day	**169**	**197**	**218**	–
Visit window (days)	**162-176**	**190-204**	**204-232**	–
BSA involvement (%), PGA, PASI [d]	X	X	X	X
LSS, mNAPSI [d]	X	X	X	X
PSI, DLQI [e]	X	X	X	X
Concomitant medication review	X	X	X	X

[a] Participants who withdraw from the study during Part B should complete the final assessments at the Early Withdrawal Visit (where relevant and when possible, this should be arranged within 72 hours of the start of a new psoriasis treatment).

[b] All participants will attend Visits 12 and 13, unless they are considered a 'treatment failure' or meet the criteria for rebound.

[c] Only participants who are classified as responders at Week 16 (Visit 10) and have not relapsed at Week 28 (Visit 13) will be eligible for Visit 14 (Week 40).

[d] Investigator rating scales. Participants will be asked to withhold all emollients or moisturizers on the day of these study visits until all study assessments are completed.

[e] Participant-reported assessments.

During the screening period, participants will be advised to monitor their psoriasis symptoms and remain on a stable regimen of topical emollients and low-dose topical corticosteroid medications (if they are already taking any). Participants will be asked to withhold the application of any emollients or moisturizers on the day of any site visit until after all study assessments have been performed. As part of the screening, PASI, BSA involvement, and PGA scores will be measured (inclusion criterion #4, Section 4.1.1).

Participants meeting eligibility criteria at screening will return to the study site on Day 1. The PASI, BSA involvement, and PGA scores must be available to reconfirm eligibility prior to randomization and administration of the first dose of study drug on Day 1 (Visit 2).

6.1 Efficacy Assessments

6.1.1 Psoriasis Area and Severity Index Score

The PASI score will be assessed as described by Langley and Ellis (2004). The PASI is a physician assessment that combines the assessment of the severity of and area affected by psoriasis into a single score in the range 0 (no disease) to 72 (maximal disease). The absolute PASI score in this study is used as part of inclusion criterion #4. The PASI percentage response rates are efficacy endpoints (ie, PASI-50, PASI-75, PASI-90, and PASI-100). For example, the percentage of participants who achieve a 75% or greater reduction in PASI score from baseline is represented by the PASI-75 value. Details of the PASI assessment will be provided in the relevant training material.

Response Definitions based on PASI score at Week 16:

- **Responders:** Participants on treatment achieving PASI-50 or greater at Week 16 visit
- **Relapse:** Increase in PASI score to baseline value or greater, or participant begins a new treatment for psoriasis
- **Partial Relapse:** Loss of PASI-50 response after cessation of study treatment
- **Rebound:** Increase in PASI score to 125% of baseline value or above, or onset of new pustular/erythrodermic psoriasis within 3 months of cessation of study treatment
- **Duration of remission:** Time from first achievement of PASI-100 to loss of PASI-100
- **Duration of treatment success:** Time from first achievement of PASI-50 to loss of PASI-50
- **Duration of therapeutic effect:** Time from cessation of study treatment until increase of PASI to 50% of maximum improvement from baseline

6.1.2 Lesion Severity Score

The LSS is used to score the severity of psoriasis plaques (Patel and Tsui 2011). The dimensions of scaling, erythema, and plaque elevation are each scored on a scale from 0 to 4, and the total LSS is the numerical sum of the 3-dimensional scores observed at a single study visit.

6.1.3 Physician's Global Assessment

The National Psoriasis Foundation Psoriasis Score version of a static PGA is calculated by averaging the total body erythema, induration, and desquamation scores (Feldman and Krueger 2005). Erythema, induration, and desquamation will be scored on a 6-point scale, ranging from 0 (clear) to 5 (severe): the total PGA score is defined as the average of the erythema, induration, and desquamation scores. Details of the PGA assessment will be provided in the relevant training material.

6.1.4 Percent of Body Surface Area Involvement

The percent of BSA involvement will be estimated for each participant, where 1% is approximately the area of the participant's handprint (Walsh et al 2013). Details of the BSA assessment will be provided in the relevant training material.

Walsh and colleagues proposed the product of the PGA and the BSA involvement as a simple and effective alternative for measuring severity of psoriasis in clinical trials (Walsh et al 2013).

6.1.5 Modified Nail Psoriasis Severity Index

The mNAPSI is a numeric, reproducible, objective, and simple tool for physicians to evaluate the severity of nail bed psoriasis and nail matrix psoriasis by area of involvement in the nail unit (Cassell et al 2007). Details of conducting the mNAPSI will be provided in the relevant training material.

6.1.6 Dermatology Life Quality Index

The DLQI is a patient reported outcomes instrument for assessing the impact of dermatologic conditions on patients' quality of life (Finlay and Khan 1994).

6.1.7 Psoriasis Symptom Inventory

The PSI is a patient reported outcomes instrument that is used to assess the severity of plaque psoriasis symptoms (Bushnell et al 2013). All symptoms (itch, redness, scaling, burning, cracking, stinging, flaking, and pain) are rated on a 5-point severity scale. The PSI demonstrated good construct validity and was sensitive to within-subject change ($p<0.0001$). Details of administering the PSI will be provided in the specific user manual.

6.1.8 Pain

Pain will be assessed by the SF-36 BPS and the VAS Pain (Hawker et al 2011).

6.1.9 Fatigue

Consistent with a recent study of fatigue in psoriasis (Skoie et al 2017), fatigue will be assessed by the vitality subscale of the SF-36 (van der Heijden et al 2003) and a fatigue VAS (Wolfe 2004).

6.1.10 Biopsy of Skin Plaque

Skin plaque biopsies (ie, a 4 mm punch biopsy, performed pre-dose by suitably trained study personnel and processed as per laboratory manual) are to be performed after all other assessments have been completed at the end of Visits 2 and 10.

6.2 Safety and Tolerability Assessments

6.2.1 Adverse Events

6.2.1.1 Definitions

6.2.1.1.1 Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to the study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a participant enrolled into this study regardless of its causal relationship to the study drug. Participants will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A TEAE is defined as any event not present before exposure to the study drug or any event already present that worsens in either intensity or frequency after exposure to the study drug.

6.2.1.1.2 Serious Adverse Events

An SAE is defined as any event that

- results in death
- is immediately life threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.2.1.1.3 Suspected Unexpected Serious Adverse Reactions

A SUSAR is a serious adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved IMP). By definition, an adverse reaction is considered causally related to the study drug.

6.2.1.1.4 Adverse Events of Special Interest

There are no prespecified AEs of special interest for this study.

6.2.1.2 Eliciting and Documenting Adverse Events

Adverse events will be reported from the date of signed informed consent and through for 28 days after cessation of dosing. Adverse events occurring after the 28 days post-treatment would only be reported if the investigator considers it to be related to the study treatment.

If the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor (or designee).

Serious AEs that occur more than 30 days after the last dose of study drug need not be reported unless the investigator considers them related to the study drug.

At every study visit, participants will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, changed concomitant medication regimens (prescription or OTC medications), noticed any changes in bowel habits, or had unplanned visits to their general practitioner since the last visit.

In addition to participant observations, AEs identified from any study data (eg, laboratory values, physical examination findings, ECG changes) or identified from review of other documents (eg, participant diaries) that are relevant to participant safety will be documented on the AE page in the eCRF.

6.2.1.2.1 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the participant's daily activities or their health. The intensity of the AE will be rated in accordance with the CTCAE version 5.0.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.2.1.2.2 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process. Regardless of the investigator's assessment of an AE's relationship to study drug, the AE must be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: There is no association between the study drug and the reported event.

Possible: Treatment with the study drug caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug but could also have been produced by other factors.

Probable: A reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.

Definite: A definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered.

6.2.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes the following:

- Dose (number of capsules per day)
- Description of the event / event term
- Date and time of onset
- Investigator-specified assessment of severity

- Investigator-specified assessment of causal relationship to study drug
- Date and time of resolution of the event
- Seriousness
- Lot/batch number
- Any required treatment or evaluations
- Action taken with the study drug due to the event
- Outcome
- Investigator-specific assessment if the AE is related to a recent/current COVID infection
- If a COVID positive PCR test received within last 14 days

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The then-current version of MedDRA will be used to code all AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an AE, but it should be captured in the medical history page(s) of the eCRF. However, it should be recorded as an AE at any time during the study that it deteriorates to a greater extent than would be expected.

If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

6.2.1.3.1 Reporting Serious Adverse Events

Any AE that meets SAE criteria (Section 6.2.1.1) must be reported to [redacted] immediately (ie, within 24 hours) after the time site personnel first learn about the event.

To report the SAE, the investigator must record the SAE on the AE eCRF in the EDC system as well as any relevant eCRF forms (eg, drug dispensation eCRF, applicable laboratory eCRF). When the AE eCRF is completed, [redacted] personnel will be notified electronically automatically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, please complete the back-up paper SAE Form and send it by e-mail to [redacted] Safety at [redacted], or call the [redacted] SAE hotline and fax the completed paper SAE Form to [redacted] within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information: [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

An investigator who receives a safety notification letter describing a SUSAR or other specific safety information from the sponsor will review and then file it as appropriate and will notify the local IRB/IEC, if appropriate according to local requirements.

6.2.1.3.2 Reporting Suspected Unexpected Serious Adverse Reactions

The sponsor will promptly evaluate all SUSARs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs/IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single SAE cases, the sponsor will assess the expectedness of these events using the approved version of the EDP1815 IB at the time of

event onset, comparing the severity of each SUSAR and the cumulative event frequency reported for the study with the severity and frequency reported in the EDP1815 IB.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the sponsor as needed. If an AE, after causality and expectedness assessment, is regarded as a potential SUSAR by the medical monitor and in agreement with the sponsor, unblinding for regulatory reporting purposes must be performed before notification of the SUSAR to the regulatory authorities and IRBs/ECs, as applicable. The procedure must ensure that the identity of the IMP is only revealed to those that need to obtain this information.

6.2.1.4 Follow-Up of Participants Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, the event is considered stable, the participant dies, or the participant is lost to follow-up.

6.2.2 Bristol Stool Form Scale

The BSFS is a classification system for the form (appearance) of human feces (O'Donnell et al 1990) that has been determined to be a reliable and validated assessment that correlates well with stool water content (Blake et al 2016). In addition, the *Prevotella* enterotype has been found to be more abundant in subjects with looser stools (Vandeputte et al 2016).

The BSFS classifies human feces into 7 consistency categories, with the highest scores corresponding to loose stools and fast colon transit and the lowest scores corresponding to hard stools (low stool water content) and slow colon transit.

During the screening period, participants will complete a 7-day stool diary over the week before the baseline visit. Participants will record in the diary the date and time of each defecation, as well as its BSFS category. Participants will bring their completed diaries to the baseline visit, when study staff will collect it for entry in the eCRF.

6.2.3 Physical Examinations

A complete physical examination will be conducted, including assessments of the skin and cardiovascular, respiratory, GI, and neurological systems. Height (at screening only) and

weight will also be measured and recorded (without shoes, street clothing). Body mass index will be calculated from the height and weight. Investigators should pay special attention to clinical signs related to previous serious illnesses.

6.2.4 Vital Signs

Blood pressure, pulse rate, respiratory rate, and temperature will be assessed. Blood pressure and pulse measurements will be assessed in a sitting position with a completely automated device. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, mobile phones).

Vital signs (to be checked prior to any procedures) will consist of 1 pulse rate and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The lowest of the 3 blood pressure readings will be recorded on the eCRF.

6.2.5 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the SoA (Table 6-1) using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTcF intervals.

At each visit, a single individual ECG tracing should be obtained: if, in the judgment of the investigator, the ECG tracing appears to be clinically significant, it should be repeated. If the repeated tracing also appears clinically significant, the investigator should report the abnormality as an AE and consult with the medical monitor to decide whether the participant should continue treatment in the study.

6.3 Pregnancy

Pregnancy is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation or up to 28 days after the final dose of study drug must be reported to [redacted] Safety by phone or email, within 2 weeks of learning of its occurrence. [redacted] Safety will send the Exposure in Utero Form to the site for completion within 24 hours. This form should be completed and returned to [redacted] Safety within 24 hours of receipt. The pregnancy must be followed up until the first “well-baby

visit" (or similarly purposed visit 6 to 8 weeks postpartum) to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the participant was discontinued from the study. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, congenital anomaly, ectopic pregnancy), the investigator should follow the procedures for reporting an SAE. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the participant has completed the study, and considered by the investigator as possibly related to the study treatment, must be promptly reported to [redacted].

6.4 Laboratory Analyses

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, vital sign measurements), including those that worsen from baseline or are clinically significant in the medical and scientific judgment of the investigator, are to be recorded as AEs or SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition, are **not** to be reported as AEs or SAEs.

Standard laboratory analyses to understand safety and tolerability include the following:

- Blood or plasma analytes: urea, creatinine, sodium, potassium, ALT, AST, total and direct bilirubin, CRP, creatine kinase, fasting glucose, fasting lipid panel (total cholesterol, HDL, LDL, triglycerides)
- Hematologic analyses: full blood count, including hemoglobin, MCV, MCH, MCHC, hematocrit, percent reticulocytes, platelet count; differential white blood cell count including neutrophils, lymphocytes, monocytes, and eosinophils
- Urinalysis by dip stick: protein, blood, glucose, ketones, bilirubin, pH, nitrites, and specific gravity

Other screening tests include the following:

- Serology (HIV antibody, HbsAg, and HCV antibody)
- Serum pregnancy test (HCG) at screening, urine test thereafter

Blood samples for assessment of fasting blood glucose and lipid panel will be obtained after the participant has fasted for at least 8 hours.

A central laboratory (or specialized central laboratories) will be used for all laboratory analyses. Details of sample collection and handling procedures will be provided in the specific laboratory manual.

The investigator must review the laboratory reports, document this review, and record any clinically relevant changes occurring during the study. If the laboratory reports are not transferred electronically, the values must be filed with the source information (including reference ranges). In most cases, clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory assessments, as defined in this section, must be conducted in accordance with the laboratory manual and the SoA (Table 6-1). Screening laboratory results will be used to confirm eligibility at Visit 2 (Baseline). If laboratory values from non-protocol-specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

6.4.1 Blood Volume

The planned maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 130 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. The planned maximum amount of blood collected from each participant at a single visit will not exceed 46 mL, and the planned maximum amount of blood collected from each participant over 30 days will not exceed 58 mL.

6.4.2 Pharmacokinetics

Systemic exposure following oral EDP1815 dosing is estimated to be very low based on lack of detection in blood (<0.01% of administered dose). However, plasma samples will be taken from all participants for the estimate of systemic EDP1815 levels by PCR with strain-specific primers that can detect EDP1815 specifically, even when other strains of *Prevotella histicola* are present. Any effects of EDP1815 on the gut microbiome will be investigated using 16S ribosomal RNA sequencing, which measures both the presence and quantity of microbes at the genus level. Sampling will be performed as specified in the SoA (Table 6-1, blood sample for systemic levels of microbes).

6.4.3 Pharmacodynamics and Biomarkers

Procedures for sample collection, processing, storage, and shipment will be detailed in the study specific laboratory manual. Biomarkers are exploratory endpoints and analytical results for biomarkers will not be included in the CSR. They will be reported separately from the CSR.

Digital photographs should be taken of up to 6 lesion sites that have a lesion area ideally greater than 2 cm by 2 cm at baseline. The same locations photographed at baseline should be followed throughout the study for each participant. Procedural details for digital photography will be provided in the specific user manual.

6.4.3.1 Histologic Assessment

A 4 mm punch biopsy will be taken by suitably trained study personnel (see Section 6.1.10). Standard histology will be performed on skin plaque biopsies (including epidermal thickness, basal mitotic counts and immune cell infiltrates, immunohistochemistry) from approximately

15 participants in each cohort. Details will be provided in the study specific laboratory manual. The histologic evaluations are exploratory and are outside the scope of the CSR.

6.4.3.2 mRNA Transcription Analysis

An mRNA transcription analysis will be performed on the skin plaque biopsies.

6.4.3.3 Blood Cytokine and Chemokine Analysis

Blood samples will be stimulated ex vivo and analyzed for levels of cytokines and chemokines, including IL-1 beta, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p40, IL-17A, TNFα, and IFNγ (ie, exploratory biomarkers).

6.4.3.4 Analysis of Fecal Microbiome

The microbiome composition of stool samples will be assessed by 16S ribosomal RNA sequencing, which looks at the diversity and abundance of microbes in the colonic microbiome (Human Microbiome Project Consortium 2012). EDP1815 is not expected to alter the composition of the microbiome, but it is being evaluated as a safety biomarker.

7 Statistical Considerations

Analysis methods for key endpoints are described below. Further details on all analyses will be described in the SAP.

No formal hypothesis will be tested. A model-based probability inference approach in a Bayesian framework will be used to guide decision-making around dose selection. Posterior estimates and 95% CrI for the difference between each active dose and placebo will be produced for relevant primary and secondary endpoints.

Unless otherwise specified, missing data will be considered as missing at random and will be accounted for using mixed models for repeated measures, with all time points collected for the relevant endpoint included in the model. This includes data which is excluded due to collection after treatment discontinuation or after a protocol deviation as applicable to the definition of the estimands used in the analysis.

The primary analysis for the study will occur after all participants have completed 4 weeks of follow-up after their last dose of study medication (end of Part A). The final analysis for the study will occur when all participants have completed the required relapse and rebound follow-up period of up to 24 weeks post-treatment (end of Part B).

7.1 Estimands and Intercurrent Events

7.1.1 Primary Efficacy Estimand

The primary estimand will be the effect of EDP1815 on the percent change in PASI score from baseline to Week 16 in the mITT set of all treated participants, regardless of deviations from the protocol. Only data collected while on treatment will be used to account for the intercurrent event of treatment discontinuation (hypothetical strategy based on adherence to treatment only). The posterior mean difference between each active dose and the pooled placebo will be estimated.

Percent change from baseline in PASI score at each visit will be calculated as:

100*(PASI score at Visit – baseline PASI score) / baseline PASI score.

A negative percentage change from baseline will indicate an improvement.

For the primary analysis, 3 supportive estimands will also be considered:

- To assess the impact of intercurrent events related to protocol deviations believed to impact efficacy, a supportive analysis will be performed where all data collected after any such identified protocol deviations will be excluded. Participants who had a protocol deviation believed to impact efficacy prior to the first dose of treatment (hypothetical strategy based on adherence to treatment and the aspects of the protocol which impact efficacy) will be completely excluded from this analysis.

- To assess the impact of treatment discontinuation for any reason, a supportive analysis will be performed in which all data collected up to the end of Week 16, including any data collected after treatment discontinuation will be included (treatment policy strategy).

- To assess the impact of treatment discontinuation due to a requirement for alternative therapy, a supportive analysis will be performed where the highest PASI score recorded prior to treatment discontinuation will be applied to all expected visits after treatment discontinuation up to Week 16.

The primary analysis will be performed using a Bayesian MMRM as fully described in Section 7.6.1. Data from visits prior to Week 16 will be included in the model and missing data will not be explicitly imputed.

Supportive analyses will also be performed in the same manner, using the 3 supportive estimands as defined above. These will explore the possible impact of the intercurrent events of treatment discontinuation for any reason, treatment discontinuation due to requirement for alternative treatment, and events relating to protocol deviations that may have an impact on efficacy.

7.1.2 Secondary Efficacy Estimands

Estimands for the analyses of all secondary endpoints are shown in Table 7-1.

Table 7-1 Summary of Secondary Estimands

Population of interest	Endpoint	Consideration of intercurrent events	Summary measure
mITT set	Mean percentage change from baseline in PASI Score at Weeks 4, 8, and 12	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active treatment group and pooled placebo at each visit
mITT set	Mean absolute change from baseline in PASI Score at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active treatment group and pooled placebo at each visit
mITT set	Achievement of PASI-50 at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior odds ratio for response between each active treatment group and pooled placebo at each visit
mITT set	Time to first achievement of PASI-50	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Hazard ratio for each active group versus placebo
mITT set	Achievement of PASI-75, PASI-90 and PASI-100 at Week 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Proportion of response for each endpoint in each treatment group at each visit
mITT set	Achievement of PGA of 0 or 1 with a ≥2-point improvement from baseline at Week 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior odds ratio for response between each active treatment group and pooled placebo
mITT set	Achievement of PGA of 0 at Week 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior odds ratio for response between each active treatment group and pooled placebo
mITT set	Mean percentage change from baseline in PGA×BSA at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active treatment group and pooled placebo at each visit
mITT set	Mean absolute change from baseline in PGA×BSA at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active treatment group and pooled placebo at each visit
mITT set	Mean percentage change from baseline in LSS at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active dose and pooled placebo at each visit
mITT set	Mean absolute change from baseline in LSS at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active dose and pooled placebo at each visit
mITT set	Mean percentage change from baseline in DLQI score at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment	Posterior mean difference between each active dose and pooled placebo at each visit

Population of interest	Endpoint	Consideration of intercurrent events	Summary measure
		discontinuation, regardless of protocol deviations	
mITT set	Mean absolute change from baseline in DLQI score at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active dose and pooled placebo at each visit
mITT set	Mean percentage change from baseline in mNAPSI total score at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active dose and pooled placebo at each visit
mITT set	Mean absolute change from baseline in mNAPSI total score at Weeks 4, 8, 12, and 16	To include all data collected prior to treatment discontinuation, regardless of protocol deviations	Posterior mean difference between each active dose and pooled placebo at each visit
Week 16 responders set	Cumulative incidence of partial relapse at Weeks 20, 24, 28, and 40	To include all data collected after treatment discontinuation	Proportion of participants to relapse in each treatment group at each visit
Week 16 responders set	Cumulative incidence of complete relapse at Weeks 20, 24, 28, and 40	To include all data collected after treatment discontinuation	Proportion of participants to relapse in each treatment group at each visit
mITT set	Cumulative incidence of rebound at Weeks 20, 24, 28, and 40	To include all data collected after treatment discontinuation	Proportion of participants to rebound in each treatment group at each visit

Summaries and analyses of the secondary endpoints are detailed in full in Section 7.6.2.

7.2 Exploratory Endpoints

The exploratory endpoints include the following:

- Percentage of participants achieving PASI-50, PASI-75, PASI-90, and PASI-100 at Weeks 4, 8, and 12
- Percentage of participants achieving PGA of 0 or 1 with a ≥2-point improvement at Weeks 4, 8, and 12
- Percentage of participants achieving PGA of 0 at Weeks 4, 8, and 12
- Mean change from baseline in PSI quality of life total and itch scores at Weeks 12 and 16

- Mean percentage change from baseline in PSI quality of life total and itch scores at Weeks 12 and 16
- Mean change from baseline in Pain and Fatigue scores at Weeks 4, 8, 12, and 16
- Mean percentage change from baseline in Pain and Fatigue scores at Weeks 4, 8, 12, and 16
- Mean change from baseline in fasting blood glucose and fasting lipid panel at Weeks 8 and 16
- Mean duration of remission in participants who achieve PASI-100
- Mean duration of treatment success in participants who achieve PASI-50
- Mean duration of therapeutic response in participants after cessation of study treatment

Biomarker endpoints (statistical analysis to appear separately from the CSR) include the following:

- Histological assessment of skin plaque biopsies (including epidermal thickness, basal mitotic counts and immune cell infiltrates) at Week 16 versus baseline
- mRNA transcription analysis on skin plaque biopsies at Week 16 versus baseline
- Blood cytokine and chemokine levels at Week 16 versus baseline
- Microbiome composition (in feces) at Week 16 and Week 20 versus baseline

Exploratory endpoints will be summarized using the mITT set, with data collected after discontinuation of treatment excluded but without consideration of any protocol deviations.

7.3 Sample Size Determination

The sample size of 225 participants in total, has been chosen to explore the tolerability and safety of EDP1815. Although the study will use a model-based probability inference approach in a Bayesian framework, the following power calculation was also performed

(using a basic frequentist approach) in order to give confidence that enough participants are available to find a clinically meaningful difference between active dose and placebo if the below assumptions are met.

The primary efficacy endpoint is the percent change from baseline in the PASI score at Week 16. Percent change from baseline relative to placebo will be estimated within the model (Section 7.6.1) as (percent change in active) - (percent change in placebo), with a negative value indicating a greater improvement for active than placebo. A percent change from baseline relative to placebo of at least 20% will be considered clinically meaningful. The pooled standard deviation across all doses is assumed to be 25%.

Participants in the placebo arm of each cohort will be pooled for the statistical analysis in order to compare active and control arms resulting in 75 participants randomized to the pooled placebo group and 50 participants randomized to each active treatment group (EDP1815 0.8×10^{11} cells, EDP1815 3.2×10^{11} cells, and EDP1815 8.0×10^{11} cells). Assuming that no more than 15% of participants will discontinue treatment before the Week 16 visit, at least 42 active and 21 placebo participants in each of the 3 cohorts are expected to provide data through the Week 16 visit.

Each pairwise comparison between pooled placebo and active dose would be expected to have more than 95% power to detect a difference between the treatment groups at the 5% significance level under the assumption that pooling the placebo groups is a valid strategy. If the 3 placebo cohorts are considered to be too heterogeneous for pooling into a single reference group, the power to detect a difference in each within-cohort pairwise comparison between active and placebo doses would be greater than 80%.

As the statistical inference for this study will focus on estimation rather than testing a formal hypothesis, no multiplicity adjustments of the different comparisons between groups in order to control the study-wise type I error rate will be performed.

Similarly, as there is no intention to use any interim analyses to stop the study early for efficacy (Section 7.6.7), no adjustments for multiplicity will be made to account for any analyses performed as part of the interim analyses.

7.4 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Enrolled set: The enrolled set will consist of all participants who sign the ICF.

mITT set: The mITT set will consist of all participants who were randomized to treatment and who received at least one dose of study treatment. Participants who withdraw from the study before the end of Week 4 and are replaced will be included in this analysis set. All analyses using the mITT will group participants according to randomized treatment.

PPS: The PPS will consist of all mITT participants who were not replaced (following study withdrawal before the end of Week 4) and who do not have a protocol deviation that may impact efficacy with a start date for the deviation before initiation of study treatment. Note that in the case of participants who have a protocol deviation with a potential impact on efficacy after initiation of treatment, the participant will remain in the PPS but all data collected after the protocol deviation occurred will be excluded from any analyses performed using the PPS. All analyses using the PPS will group participants according to treatment received at the start of the study. Deviations that may affect efficacy are shown in Table 7-2.

Week 16 responders set: The Week 16 responders set will consist of all mITT participants who achieved a PASI-50 response at Week 16.

Safety set: The safety set will consist of all participants who received any study drug. All analyses using the safety set will group participants according to treatment received. If participants received multiple treatments during the study, they will be assigned to treatment group in the following manner:

- If participant received both active EDP and placebo treatments, they will be assigned to the active treatment group.
- If participant received 2 or more different active dose levels, they will be assigned to the treatment they received for the longest period.

The mITT set will be the primary population of interest for the efficacy section, with some supportive analyses performed using the PPS. The safety set will be used for all safety summaries.

Table 7-2 Deviations with a Potential Impact on Efficacy

Description	Evaluation Period	Impact on PPS analyses
Not meeting inclusion criteria 3, 4, or 6 or meeting any of exclusion criteria 1-12 or 27	Baseline	Exclude participant from PPS.
Use of any prohibited medication (Section 5.8.2.1)	Throughout study	If start date of prohibited medication ≤ date of first dose of study drug then exclude participant from PPS. Otherwise, include participant in PPS but exclude all data collected on or after start date of prohibited medication.
Compliance with study drug <80%	Evaluated in 8-week periods (Weeks 1-8 and 9-16)	If participant is non-compliant within Week 1-8 treatment period, then exclude from PPS. If participant is non-compliant only within Week 9-16 treatment period, include participant in PPS but exclude all data collected after the Week 8 visit date.
More than 7 consecutive days with no study medication without participant being permanently withdrawn from study medication	Throughout study	Participant will not be excluded from PPS, but all data collected after the 8th consecutive day with no study medication will be excluded.
More than 14 total days with no study medication (does not need to be continuous)	Throughout study	Exclude participant from PPS.
Incorrect study treatment taken	Throughout study	Participants will not be excluded from PPS. If a participant received a study drug other than that received at the start of the study, then exclude all data collected on or after the date at which the treatment change occurred.
Study treatment blind broken	Throughout study	If participant's blind is broken prior to first dose of study drug then exclude from PPS. Otherwise, include participant in PPS but exclude all data collected on or after the date on which the blind was broken.

7.5 Description of Subgroups to Be Analyzed

Results may be summarized by individual cohort.

Subgroup analysis of the primary estimand will be performed based on the following subgroups:

- Baseline PASI score (<10, ≥10)
- Baseline PGA score (2, 3)
- Baseline BMI (<30 kg/m^2, ≥30 kg/m^2)

If the placebo groups from the 3 cohorts are found to be too heterogeneous to be pooled (Section 7.6.1), the primary and secondary analyses will be performed using within-cohort comparisons of active and placebo treatments, and summary tables may also be produced by cohort.

7.6 Statistical Analysis Methodology

Statistical analysis will be performed using SAS software Version 9.3 or later.

In addition to the inferential analyses described in Sections 7.6.1 and 7.6.2, descriptive statistics will be provided to summarize all endpoints by treatment group.

Continuous variables will be summarized using the mean, standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Time-to-event variables will be summarized using Kaplan-Meier estimates of the proportion of participants with the event at each visit. Data will be listed in data listings.

Details of the statistical analyses, methods, and data conventions will be described in the SAP.

7.6.1 Analysis of Primary Efficacy Endpoint

The assumption that the 3 cohorts of placebo participants can be pooled into a single placebo group to be used as a control for all active doses will be examined using mean (±SD) plots and box plots of percent change in PASI score against time. In addition, an MMRM will be used to compare the 3 cohorts of placebo participants. The model will include parameters for cohort, visit and baseline PASI score together with cohort*visit and baseline PASI score*visit interactions. Least squares mean (95% CI) estimates for each placebo cohort will be plotted by visit.

A decision will be made by the Evelo study team, based on examination of the above figures and model, on whether the pooling strategy is appropriate.

The primary analysis will be performed using a Bayesian MMRM. The model will include parameters for treatment*visit and baseline PASI score*visit interactions. Body mass index, gender, country, and time since diagnosis will also be considered and included as parameters if found to be significant ($p<0.05$). The model will not include an intercept. Visit will consist of 6 levels (Weeks 1, 2, 4, 8, 12, and 16) and treatment will consist of 4 levels (pooled placebo, EDP1815 0.8×10^{11} cells, EDP1815 3.2×10^{11} cells, and EDP1815 8.0×10^{11} cells) if the placebo pooling strategy is considered appropriate or 6 levels (Placebo matching EDP1815 0.8×10^{11} cells, Placebo matching EDP1815 3.2×10^{11} cells, Placebo matching EDP1815 8.0×10^{11} cells, EDP1815 0.8×10^{11} cells, EDP1815 3.2×10^{11} cells, and EDP1815 8.0×10^{11} cells) if the placebo pooling strategy is not considered appropriate.

The priors for all parameters in the model will be non-informative and follow a normal distribution with mean 0 and SD 1000. The prior for the variance-covariance matrix will follow an inverted Wishart distribution with degrees of freedom equal to the number of visits and an identity scale matrix. The choice of Wishart distribution is based on it being the conjugate prior of the inverse-covariance matrix of a multivariate-normal random vector.

If the assumption of similarity between the 3 placebo cohorts is considered appropriate, the placebo cohorts will be pooled, and a single placebo control group will be used for the pairwise differences for each active dose to placebo. If the assumption of similarity is considered inappropriate, each placebo dose will be included in the model as a separate dose level and pairwise comparisons between each active dose and placebo will be performed using only the matching placebo dose data for the relevant active dose.

The adjusted posterior mean percentage change from baseline and the associated 95% HDP CrI for each treatment at Week 16 will be reported, together with the adjusted mean difference from placebo and the associated 95% HDP CrI for each active dose at each visit and the probability that each treatment difference is less than 0%, -20%, -30%, and -50%.

Model checking and diagnostic plots, including posterior density plots of the posterior samples for all parameters in the model and residual plots to evaluate the distributional assumptions underlying the model, will be produced. The assumption that data are missing at random will be evaluated by plotting the mean percentage change in PASI score against visit,

by treatment group, for the subgroups of participants who completed 16 weeks of study drug compared with those who discontinued study drug before the Week 16 visit.

If model checking and diagnostic plots show a violation of the assumptions underlying the analysis, alternative statistical methods will be considered, appropriate to the type of violation observed.

This primary analysis will be repeated using the 3 supportive estimands defined in Section 7.1.1.

If the assumption of similarity between the placebo cohorts is supported, a supplementary analysis will be performed on the percent change from baseline to Week 16 in PASI score using a dose-response model on the pooled cohorts. The log-linear, 3-parameter, and 4-parameter E_{max} models will be fitted and compared, with the best fitting model (lowest DIC) selected for use in the outputs.

The dose-response model will be fitted to the data using Bayesian techniques with noninformative priors for E_0 and E_{max} and an FUP for ED50 (3- and 4-parameter models only) and the slope parameter m (4-parameter model only). The rationale for this choice of inference is that the FUP shrinks the dose response towards a flat line throughout the dose range, therefore providing more conservative estimates of the dose-response relationship compared to maximum likelihood (Bornkamp 2014). The models will be fully described in the SAP.

Based on the selected model, the posterior mean with associated 95% HDP CrI, for the difference from placebo for each active dose will be produced for the pairwise differences between each active dose and placebo, together with the posterior mean and 95% HDP CrI of the treatment difference from placebo for each active dose and posterior probabilities that difference from placebo is less than 0, -20%, -30%, and -50%. A further sensitivity analysis will be performed on the dose response model, in which participants who withdrew from study drug due to treatment will have their Week 16 percentage change from PASI imputed as 100% after study drug was discontinued.

Percent change from baseline in PASI score will be summarized by visit.

All summaries and analyses defined above for the primary estimand will be repeated using the subgroups defined in Section 7.5.

7.6.2 Analysis of Secondary Efficacy Endpoints

All secondary analyses will be performed either using the pooled placebo group if the assumption of similarity for the placebo cohorts is considered appropriate or using the 3 cohort-level placebo groups if it is not considered appropriate.

Unless otherwise specified, all secondary analyses will be performed on the mITT set, excluding data collected after treatment discontinuation, without consideration of any protocol deviations. Dose will be treated as a categorical variable and no dose response modelling will be done. Comparisons of interest will be between individual EDP1815 doses and placebo. All p-values, posterior probabilities, CI, and CrI calculated will be considered as descriptive with no further adjustments for multiplicity performed.

Data will be analyzed as collected and no imputation of missing data will be performed.

The covariates selected for the Bayesian MMRM analysis for the primary estimand will also be used in all other analytical models including covariates.

Mean percentage change from baseline in PASI score at Weeks 4, 8, and 12 will be analyzed as part of the MMRM for the primary estimand. The same statistics produced for the Week 16 time point will also be produced at Weeks 4, 8, and 12.

The following secondary endpoints will be analyzed in the same manner as described for the primary analysis:

- Mean absolute change from baseline in PASI score at Weeks 4, 8, 12, and 16
- Mean percentage change from baseline in LSS at Weeks 4, 8, 12, and 16
- Mean absolute change from baseline in LSS at Weeks 4, 8, 12, and 16
- Mean percentage change from baseline in PGA×BSA at Weeks 4, 8, 12, and 16
- Mean absolute change from baseline in PGA×BSA at Weeks 4, 8, 12, and 16

- Mean percentage change from baseline in DLQI score at Weeks 4, 8, 12, and 16
- Mean absolute change from baseline in DLQI score at Weeks 4, 8, 12, and 16
- Mean percentage change from baseline in mNAPSI total score at Weeks 4, 8, 12, and 16
- Mean absolute change from baseline in mNAPSI total score at Weeks 4, 8, 12, and 16

For the PASI-50, a generalized linear mixed effects model with a logit link function will be fitted using data from all visits. Treatment, visit, and baseline PASI score terms will be included in the model as fixed effects, together with treatment*visit and baseline PASI score*visit interactions, and any baseline covariates selected in the primary analysis model for the primary estimand. Odds ratios and 95% CIs for each active dose compared to placebo at each visit will be presented.

A supportive analysis for the PASI-50 will also be performed, in the same manner as described above, in which participants who withdraw from study drug before Week 16 due to requirement for alternative therapy will be included in the model with the PASI-50 endpoint imputed as 'not achieved' at all expected visits after study drug withdrawal.

A sensitivity analysis will also be performed on the PASI-50. Bayesian logistic regression models will be individually fitted at each of Weeks 4, 8, 12, and 16. The model will include parameters for treatment and baseline PASI score together with any baseline covariates selected in the primary analysis model for the primary estimand. The posterior odds-ratios for each pairwise comparison of an active EDP1815 dose and placebo with associated 95% HDP CrI will be presented together with the posterior probability that the true odds ratio >1.

Percentage of participants achieving PGA of 0 or 1 with a ≥2-point improvement and percentage of participants achieving a PGA of 0 will be analyzed in the same manner as described above for PASI-50 with the exception that the sensitivity analysis using the Bayesian logistic regression model will only be fitted on the Week 16 data.

For the time to first achievement of PASI-50, a nonparametric survival analysis for interval censored data will be performed. The expectation-maximization iterative complex minorant (EMICM) method for iterative computation of the nonparametric maximum likelihood

estimator for the survival function (Wellner and Zahn 1997) will be used. The number and proportion of participants who meet the PASI-50 at least once during the study will be presented. A generalized log-rank test will be used to compare each active dose with placebo and the p-value for treatment difference will also be presented. The estimated survival curves for each treatment group will also be presented.

Cumulative incidence of partial relapse and complete relapse at Weeks 20, 24, 28, and 40 will be summarized by treatment group on the Week 12 responders set.

Cumulative incidence of rebound after cessation of study treatment at Weeks 20, 24, 28, and 40 will be summarized by treatment group.

7.6.3 Analyses of Exploratory Efficacy Endpoints

Exploratory endpoints will be summarized using the mITT population, with data collected after discontinuation of treatment excluded but without consideration of any protocol deviations. Details of all analyses to be performed on the exploratory endpoints will be detailed in the SAP.

Analyses of biomarkers will be addressed in a data analysis plan outside the study SAP.

A further exploratory analysis will be performed on the Week 16 results. Adjusted indirect comparisons, pivoted around placebo, will be performed against publicly available data from two studies in apremilast in mild/moderate or moderate psoriasis. Further details will be provided in the study SAP.

7.6.4 Pharmacokinetic Analyses

The number and percentage of participants who have a quantifiable concentration of EDP1815 in their blood sample will be summarized using the safety set by visit. Placebo participants will be pooled into a single treatment group. If at least 20% of participants within a treatment group are found to have a quantifiable level at one of the visits, then the concentration will be summarized as a continuous variable for the relevant treatment group at that visit.

7.6.5 Safety Analyses

All safety endpoints will be tabulated or plotted by treatment group using the safety set. All safety analyses will use the pooled placebo group. Further details will be described in the SAP.

7.6.6 Other Analyses

Tabulations will be provided for completion/withdrawal status, protocol deviations, study populations, demographic and other baseline characteristics, use of concomitant medications, and exposure of and compliance with study drug.

7.6.7 Interim Analyses

An interim analysis may be undertaken during the conduct of the study after at least 50% of participants have completed at least 12 weeks of treatment or withdrawn from treatment. The purpose of this analyses will be to aid in the planning of future studies and for a better understanding of the benefit/risk profile of EDP1815.

For the interim analysis, unblinded aggregate results will be produced by an unblinded team within [redacted] and reviewed by Evelo personnel for strategic planning use. These will not be shared with any study site staff, participants, or clinical monitors who will be involved in the collection and review of individual study data.

The interim analysis will look at the primary endpoint of percentage change from baseline in PASI score, secondary, and safety endpoints. The posterior predictive probability (Spiegelhalter et al 2004) of the percent change from baseline in PASI score being at least 20% lower in each active dose compared to the pooled placebo will also be calculated, using the estimates of treatment difference found at Week 12 using the Bayesian MMRM described for the primary analysis. If the posterior predictive probabilities for all active doses are found to be <30%, then the study may be stopped for futility.

No decisions regarding study conduct, other than the potential to stop the study early for futility, will be made based on these assessments and the study will not be stopped if superior efficacy is found. Outputs featuring unblinded treatment assignments will be created by the unblinded analysis group within [redacted] and shared with selective Evelo personnel (to be included in the data dissemination plan).

Further details of the outputs that will be produced will be described in the SAP.

8 Data Quality Assurance

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management. The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

The sites will maintain source documentation and enter participant data into the eCRF as accurately as possible and will rapidly respond to any reported discrepancies. Electronic CRFs are accessed through Medidata Rave® (Medidata Solutions Inc, New York, New York). This EDC system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual username and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. A quality review of the data will be performed by the site with additional reviews by the clinical monitor through source data verification.

Each eCRF is presented as an electronic copy, allowing data entry by site staff, who can add and edit data, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed by the investigator. This system provides site staff, monitors, and reviewers with access to hard copy audits, discrepancy reviews, and investigator comment information.

After all data reviews and query resolutions are complete, the SAP is approved and signed, and any summary/analysis populations are approved, the database will be locked.

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the participants treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include diaries, laboratory reports,

ECG strips, etc. Electronic devices will be used for the administration of investigator and participant responses to Clinical Outcome Assessments. Data collected via these devices will be uploaded directly to a central database for storage and analysis. Details will be provided in the specific user manual.

All eCRF information is to be completed. If an item is not available or is not applicable, this fact must be indicated. Blank spaces must not be present unless otherwise directed. Study site personnel will enter participant data into the Medidata Rave system. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable [redacted] standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data). Adverse events and medical history will be coded using the then-current MedDRA terminology. Concomitant medications will be coded using the most current available WHO Drug Dictionary.

After database lock, each study site will receive an electronic copy of their site-specific eCRF data as entered into the EDC system for the study, including full discrepancy and audit history. Additionally, an electronic copy of all the study site's data from the study will be created and sent to the sponsor for storage. [redacted] will maintain a duplicate electronic copy for their records. In all cases, participant initials will not be collected or transmitted to the sponsor.

9 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

Country regulations, US federal regulations, and the ICH guidelines require that approval be obtained from an IRB or IEC before participation of human participants in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant or the participant's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): GCP and with applicable regulations in the countries where the study will be conducted will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals must be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to participants.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable country and local regulations.

9.3 Participant Information and Consent

A written informed consent in compliance with regulatory authority regulations or US Title 21 CFR Part 50 shall be obtained from each participant before entering the study or performing any unusual or nonroutine procedure that involves risk to the participant. An informed consent template may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB/IEC

submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the study, all active participants must be reconsented by signing the revised form.

Before recruitment and enrollment, each prospective participant or his or her legal guardian will be given a full explanation of the study, be allowed to read the approved ICF, and have any questions answered. Once the investigator is assured that the participant/legal guardian understands the implications of participating in the study, the participant/legal guardian will be asked to give consent to participate in the study by signing the ICF. The authorized person obtaining the informed consent also signs the ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research (if applicable) and explain/address the exploratory research portion of the study. Participant medical records need to state that written informed consent was obtained.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the participant or legal guardian.

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant (or the participant's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the FDA, or the IRB/IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the investigation and for 1 year following the completion of the study.

Neither the sponsor nor [redacted] is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor [redacted] is financially responsible for further treatment of the participant's disease.

10.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) Section 8.2 and Title 21 of the CFR by providing all essential documents.

10.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of participants begins.

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

10.5 Adverse Events and Study Report Requirements

The investigator agrees to submit reports of SAEs to the sponsor and/or IRB/IEC according to the timeline and method outlined in the protocol (Section 6.2.1.3.1). In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

10.6 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution. Also, the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and provide the sponsor and regulatory authority(ies) with any reports required.

10.7 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. No records may be transferred to another location or party without written notification to the sponsor.

10.8 Publications and Results Disclosures

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be

responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

11 Study Management

The study administrative structure is presented in Table 11-1.

Table 11-1 Study Administration

Role	Name/Affiliation/Address
Sponsor	Evelo Biosciences Inc. 620 Memorial Drive, Suite 500 Cambridge, MA 02139 USA
Sponsor Contact	[redacted]
Contract Research Organization	[redacted]
Study Medical Monitor (study participant management)	[redacted]
Central Laboratory	[redacted]
Serious Adverse Event Reporting	[redacted]
Lead Statistician	[redacted]

11.1 Monitoring

11.1.1 Safety Review Committee

There will be no safety review committee or data monitoring committee.

11.1.2 Monitoring of the Study

This study will be monitored according to an approved monitoring plan based on the objectives, purpose, design, and complexity of the study. The investigator will allocate adequate time for all monitoring visits and between visits to facilitate the requirements of the study and study timelines. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given direct access to all study-related documents and study-related facilities (eg, pharmacy, diagnostic laboratory), phone, fax, and internet and has adequate space to conduct the monitoring visit. Site monitoring is conducted to ensure that the rights of human participants are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the study uses high quality data collection processes. The monitor will evaluate study processes based on Evelo or designee standards, ICH E6, and all applicable, regulatory guidelines.

11.1.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (eg, FDA or other regulatory agency) access to all study records.

The investigator should promptly notify the sponsor and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in the required procedures defined in this protocol, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by

the sponsor or designee. Amendments to the protocol (including emergency changes) must be submitted in writing to the investigator's IRB/IEC, along with any applicable changes to the ICF, for approval before participants can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol or to local regulations or ICH GCP guidelines that may or may not result in a significant, additional risk to the participant or impacts the integrity of study data.

The investigator or designee must document and explain in the participant's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard/safety risk to study participants without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, where required.

In order to keep deviations from the protocol to a minimum, the investigator and relevant site personnel will be trained in all aspects of study conduct by the sponsor/sponsor representative. This training will occur either as part of the investigator meeting or site initiation. Ongoing training may also be performed throughout the study during routine site monitoring activities.

11.3 Study Termination

Although Evelo has every intention of completing the study, Evelo reserves the right to discontinue the study at any time for clinical or administrative reasons.

If the study is prematurely terminated or suspended, the sponsor or investigator shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

The EOS is defined as the date on which the last participant completes the last visit (includes follow-up visit).

11.3.1 Study Halting Criteria

The study will be halted if any of the following occur:

- One death considered definitely, probably, or possibly related to the study drug
- Two or more participants with an SAE considered definitely, probably, or possibly related to the study drug
- Three or more participants with grade 3 AEs of the same type considered definitely, probably, or possibly related to the study drug

11.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the final data are summarized and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the CSRs in marketing applications (as applicable) meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of CSRs.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the CSR. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the final report, the sponsor will provide the investigator with the summary of the study results. The investigator is encouraged to share a summary of the results with the study participants, as appropriate. The study results will be posted on publicly available clinical trial registers.

12 References

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13 Appendices

13.1 Appendix: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Women of Child-Bearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, an FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study.

Contraception Guidance:

Male participants

Male participants must participate according to one of the following criteria:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Use a male condom during each episode of penile penetration during their participation in the study and for 90 days after the last dose of study drug. In addition, male participants must refrain from donating sperm for the duration of the study and for at least 90 days following their final visit.
- Have had a vasectomy, and the absence of sperm has been confirmed in the ejaculate.

Female participants

Female participants of child-bearing potential are eligible to participate if they agree to use a highly effective contraceptive method consistently and correctly as described in Table 13-1.

Table 13-1 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly*.
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation[b] • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal sterilization

Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Table Notes: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case, a highly effective method of contraception plus condoms should be used during their participation in the study up to and including at least 1 complete menstrual cycle (≥28 days) for women and 90 days for men post last dose.

Pregnancy Testing:

- A WOCBP should only be included after a negative serum HCG pregnancy test.
- Pregnancy testing is required at screening, randomization, and 14 days after the last dose at the follow-up visit.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information:

For male participants with partners who become pregnant:

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies to all male participants who receive EDP1815.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the

pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

For female participants who become pregnant:

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study drug by the investigator will be reported to the sponsor as described in Section 6.2.1.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study drug.

13.2 Appendix: World Health Organization Classification of Topical Corticosteroids

The potency of a topical corticosteroid depends on the formulation. Potency is also increased when a formulation is used under occlusive dressing or in intertriginous areas. In general, ointments are more potent than creams or lotions.

Table 13-2 WHO Classification of Topical Corticosteroids

Ultra-High Potency
Group I
Clobestasol propionate cream (0.05%)
Diflorasone diacetate ointment (0.05%)
High Potency
Group II
Amcinonide ointment (0.1%)
Betamethasone dipropionate ointment (0.05%)
Desoximetasone (cream or ointment) (0.025%)
Fluocinonide (cream, ointment, or gel) (0.05%)
Halcinonide cream (0.1%)
Group III
Betamethasone dipropionate cream (0.05%)
Betamethasone valerate ointment (0.1%)
Diflorasone diacetate cream (0.05%)
Triamcinolone acetonide ointment (0.1%)
Moderate Potency
Group IV
Desoximetasone cream (0.05%)
Fluocinonide acetonide ointment (0.025%)
Hydrocortisone valerate ointment (0.2%)
Triamcinolone acetonide cream (0.1%)

Moderate Potency (continued)
Group V
Betamethasone dipropionate lotion (0.02%)
Betamethasone valerate cream (0.1%)
Fluocinonide acetonide cream (0.025%)
Hydrocortisone butyrate cream (0.1%)
Hydrocortisone valerate cream (0.2%)
Triamcinolone acetonide lotion (0.1%)
Low Potency
Group VI
Betamethasone valerate lotion (0.05%)
Desonide cream (0.05%)
Fluocinolone acetonide solution (0.01%)
Group VII
Dexamethasone sodium phosphate cream (0.1%)
Hydrocortisone acetate cream (1%)
Methylprednisolone acetate cream (0.25%)

Source: Bolognia JL, Jorizzo JL, Schaffer JV. Glucocorticosteroids. Dermatology. 3rd ed. 2012. Ch 125, 2075-88.